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ORIGINAL ARTICLES.

NOTES ON THE DIAGNOSIS OF BRONCHOPNEUMONIA AND
ITS COMPLICATIONS.

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REFERENCE to any standard text will lead to the inference that primary bronchopneumonia in adults is not a common disease. That it is the usual type of pneumonia in children is accepted as well as that "terminal pneumonias" are commonly of the catarrhal variety. But that bronchopneumonia is at all confined to the extremes of life, childhood and old age is, I believe, incorrect. It will be the purpose of this paper to present evidence indicating the frequency of this type of pneumonia, to discuss the several pathologic and clinical pictures that may be grouped under the generic heading of broncho- or lobular pneumonia and their more serious complications.

In assuming a position which may seem at variance with usual conceptions of incidence, an explanation is appropriate as to why bronchopneumonia may at times escape detection and be passed over as simple bronchitis. The explanation is simple: (1) the physical signs are frequently transitory, and (2) the patient may not seem sick—that is, sick enough to excite careful examination. Pneumonia is closely associated in our mind with a group of rather definite symptoms and, in the absence of these, the examination made is liable to be either perfunctory or entirely omitted. The

fleeting, evanescent character of the physical signs can hardly be appreciated unless one has experience in ward-teaching. Time and again the signs found at morning rounds were gone in the area marked when the patient was shown at the afternoon clinic, and this explains the development of hospital routine regarding radiograms. The instructor was at times in sore need of demonstrable evidence. From this the logical step was natural of radiographing many cases of "simple bronchitis" in which no sign of consolidation had at the time been noted. The results of these examinations were illuminating; at first in revealing what we did not detect and later in confirming a suspected lesion. What interpretation is to be placed upon a record of this sort? A healthy man of twenty-six years was admitted to hospital January 20 complaining of a cold which he attributed to a wetting two days before. He had felt a little feverish the night before admission, but not sick. He said he did not feel sick enough to be in bed, but a "bit fagged." His temperature was 101°, respiration 22, pulse 90. Examination showed only rales scattered throughout both lungs: No dulness; no change in breath sounds; pectoriloquy absent. A radiogram taken on the day of admission showed an area of density, the size of an egg, just above the heart shadow in the left chest an inch from the hilus of the lung. On January 22 the shadow was still present: the patient had improved and the fever had gone. A final plate, taken on January 28, showed only a slight residual clouding in the area mentioned. At no time had there been physical signs other than those of a bronchitis (rales): at no time had the patient seemed or felt really ill. A repetition of this experience over and over gave ground for the hospital dictum—"bronchitis is rarer than a bronchopneumonia"—and this apparently extravagant assertion accords with my experience in private practice. That the patient may not feel sick, nor look more so than one does with a cold, that the temperature is but slightly elevated is sufficient explanation for neglect of searching examination. History records the "incidence of most diseases has increased with their recognition."

Not only is bronchopneumonia a very common disease in hospital practice, but the incidence will be found high among healthy young men in colleges, as I have had opportunity to observe, and it was one of the common diseases in the cantonments at periods when no epidemic prevailed. Furthermore the nature of disorders which are traced back to "colds" would be best explained by pneumonia, and these disorders are not few.

Bronchopneumonia, as the name indicates, is very often purely an extension of an infection from the smaller bronchi to contiguous pulmonary tissue. The disease seems to have been first described by Bartels, although Laennec mentioned the scattered areas of infiltration found in some cases of catarrhal bronchitis. Common usage has made the terms bronchopneumonia and lobular pneu-

monia synonymous. Some pathologists, however, draw distinctions which are not generally accepted, and until the processes are better understood in their mode of production, are useless. The morphology of broncho- or lobular pneumonia is determined largely by the type of infection, and, to some extent at least, by whether the infection enters through the respiratory tract or the blood stream. The more general aspects which characterize the pathology of lobular pneumonia have a common basis in all types. On section of the diseased lung the fresh surface has a notably "patchy" character; certain areas are raised, and at the center of these areas may usually be found the bronchi, seen as grayish spots from which pus may be expressed. The involved areas may be numerous and discrete, or they may coalesce into large consolidations; even when a considerable portion of a lobe is involved in the consolidation the picture does not often resemble lobar pneumonia. The cut surface is less granular and there is not liable to be much fibrin or leukocytic detritus as with lobar pneumonia. Between the areas of consolidation atelectasis occurs, due to stoppage of the bronchioles, with resorption of air and resulting collapse of the alveoli. In its earliest stage scattered areas of bronchopneumonia may appear as numerous discrete, minute tubercles, shotty to feel, gray or brownish in color, and surrounded by areas of reddish atelectatic tissue. When the lung presents this picture at necropsy it may be mistaken for miliary tuberculosis (and the radiogram is equally misleading). A later stage represents the enlargement of these small areas with coalescence. Thus a whole lobe may be involved, but the patchy character of the cut surface is usually preserved: massive, confluent, lobular pneumonia. Minor differences are determined, it seems, by the nature of infection and the resistance of the individual. The salient fact in this pathologic process is that it takes origin in a bronchiole. Following a bronchus into a diseased portion of the lung by dissection discloses that the consolidation is terminal or lateral to a bronchus.

Bronchopneumonia is usually thought of as a complication of typhoid fever ("typhoid pneumonia"), measles, diphtheria and occasionally of scarlet fever. The causative infecting agents are numerous. With the primary type of bronchopneumonia the pneumococcus is often found, even Type I pneumococci has been repeatedly isolated from sputum of some of my cases. Pneumococcus type IV is more common, while probably a majority of the cases of lobular pneumonia are due to streptococci, either as a primary infection or mixed with some other organism. The role of the streptococcus in these processes is by no means clear, in spite of the fact that it has been repeatedly isolated from both the sputum and from the lung tissues of cases dead of pneumonia. The reason for some doubt rests in the conception that the streptococcus infections are prone to be secondary. Weichselbaum illustrated the point

years ago with reference to empyema, which may, in the initial stage, show only pneumococci in the pus; later the pneumococci are overgrown and disappear and the pus contains only streptococci.¹ For example, measles pneumonia, a typical secondary infection, is predominantly a streptococcus pneumonia. The primary invader may be an organism of relatively slight virulence, but, given a predisposition, the tissues are made vulnerable by this trivial infection and the streptococcus finds a suitable environment for growth. Coryza is often due apparently to an invasion of the *Micrococcus catarrhalis*, an organism of weak pathogenicity, a secondary infection with streptococcus takes place and pneumonia develops. This expresses the present conception of the mode of origin of a group of diseases due to streptococcus infections, and it is the sole scientific basis for the face mask so much used in military hospitals; protecting an individual susceptible on account of some slight infection from inhaling streptococci thrown out by persons already infected. The practical difficulty in this prophylaxis is that so many healthy persons harbor *Streptococcus hemolyticus* in the throat. Mathers found hemolytic streptococci in the throats of 70 per cent. of a healthy organization at Camp Meade. These questions have not only scientific interest, but are in the front rank of practical considerations when diseases such as measles are to be cared for. For some time pediatricists have recognized that the incidence of pneumonia complicating measles is higher in even very good hospitals than among children cared for in their homes, and an impression growing toward conviction is notable that, under certain conditions, pneumonia may spread as a contagion in measles wards. The factor that is outstanding in my experience in determining the incidence of pneumonia complicating measles is the season of the year; in the cold months there has been a higher percentage of pneumonia than occurred in the warm parts of the year, and this has been true even with the most rigid methods of individual isolation. Is the body's resistance so generally lowered by cold weather?

The factors which predispose to pneumonia may be classed under two headings: those which lower the vitality of the individual and those which lower the resistance of the pulmonary tissues. Under the first heading would come not only the diseases generally recognized as terminating with bronchopneumonia, chronic and cachectic diseases and certain acute infections, such as the exanthemata, but also those conditions which suddenly reduce immunity, and here fatigue takes first place. With sound, healthy individuals no factor seems to be so potent in lowering resistance to infection as is fatigue. Probably this is in some degree true of all infections; it can hardly

¹ The advent of filtrable viruses further complicates the question and postpones definite decision. In relation to this question, see the communication of Roux to the Académie des Sciences, at the November meeting, 1918, dealing with pathogenesis of influenza.

be controverted in relation to pneumonia. Other factors of significance are hunger and chilling from exposure. All of these factors more or less enter into consideration with all types of pneumonia, lobar as well as lobular. In one case the invasion is prompt and sudden and lobar pneumonia develops; in another, more insidious or perhaps in the beginning milder, a "simple cold" with bronchopneumonia later.

Of the factors which lower the resistance of pulmonary tissues mild and even trivial infections are paramount: trivial infections are ignored. It was notable in all cantonments that those organizations that sent their cases of minor sickness to hospital had the lowest incidence of pneumonia. The significance is clear: with a mild bronchitis a bed is the best prophylactic against pneumonia. The resistance of pulmonary tissues to infection is also lowered by mechanical and chemical irritation; dust, especially sand, gases and smoke, ether and chloroform. Postoperative pneumonia is due evidently to several factors: the technical skill of the operator, the purity of the ether and skill of administration and the care of the patient during the period while he is recovering from the anesthetic, especially respecting warmth. In several clinics, where opportunity has come to me to study many cases of pneumonia following operation, I have not been able to trace the cause nearer than outlined above. The question is important and deserves more careful study than has been given to it.

In *resume*, it may be briefly stated that any circumstance which lowers the vitality of the organism as a whole, or by irritation injures the pulmonary tissues, locally, predisposes to pneumonia. The invader is always at hand and the invasion depends upon the host.

Symptoms. The clinical picture of bronchopneumonia is most variable. At one extreme is the case with signs and no symptoms other than fever, at the other extreme is a clinical picture of the severest form of pneumonia. In truth, there are cases with marked symptoms and no corresponding signs, and others with slight symptoms and clearly defined signs. The mild cases offer some difficulty in diagnosis and are often overlooked, although deserving attention on account of the frequent sequelæ. It so often happens that the patient seeks help only on account of an annoying cough. With scarcely any pyrexia the tendency is natural to dismiss the case as one of acute bronchitis requiring no thorough examination of the lungs. Allowed up and about, perhaps at work, the patient's condition becomes serious before its nature is recognized. I have known this to occur not infrequently. The patient then takes to his bed only when exhausted or in collapse. With pneumonia little enough can be done for the patient other than securing him rest and protection of his vitality, and this should not be delayed.

Occasionally the period of active infection is passed before the

patient consults a physician. A number of cases belonging in this category have been encountered where relief was sought from a persistent cough following a "hard cold," and examination disclosed an area of consolidation, but no fever or other sign or symptom. Delayed resolution of this sort may be, and often is, mistaken for a tuberculous consolidation. A young physician consulted me for a confirmation of the diagnosis of pulmonary tuberculosis made by a specialist. The patient had had a severe bronchitis some two weeks before but had kept at work in spite of fever. The physical signs were confined to an area in the upper portion of the left lower lobe—a consolidation a couple of inches in diameter. This spot slowly resolved in the course of a month. With vigorous, sthenic individuals, bronchopneumonia is, I am convinced, occasionally experienced as a "bronchial cold," and with no more results.

The onset is occasionally sudden, resembling in this respect lobar pneumonia; more often there is a gradual development, commencing as a "cold," with slight cough, becoming more severe until the patient is driven to his bed. Pleural involvement occurs late in contrast to lobar pneumonia. In the early period of the disease the temperature may not be above 101° F., the pulse but slightly increased and the respirations not accelerated. Drenching sweats are common; cough is annoying and exhausting. The sputum varies; there may be considerable amounts of mucopurulent material, with no obvious admixture of blood—with other cases the sputum is greenish pus, or, again, it resembles brick dust in color. When the infection is severe, dyspnea is often a striking symptom, and this, with the marked cyanosis, recalls the old name of the disease "suffocative catarrh." With many cases death appears to result from asphyxia rather than from a wearing out of the myocardium, as in lobar pneumonia.

The nervous symptoms are most striking. Delirium is common, not of the low, muttering type, but violent, often maniacal. A peculiar typhoid state with delirium, marked tremor and coma vigil is occasionally noted. Many patients complain of excruciating headache, and with this signs of meningismus are frequent. Relief is often prompt, following lumbar puncture and the removal of a half ounce of fluid. Headache with a stiff neck and a suggestive Kernig sign is an indication for lumbar puncture. The fluid in these conditions is under considerably increased pressure—the first half-ounce running so fast the drops cannot be counted. I have gained the impression that with some of these cases not only does the headache abate, but respiration is improved by relieving the intracranial pressure.

With severe bronchopneumonia the picture at times presented by the patient when the disease is at its height differs in many respects from lobar pneumonia. The deep, livid cyanosis arrests attention. The picture of suffocation with an excited, alert mental

state; the sweating; cold, clammy extremities in spite of a strong, regular pulse—a clinical picture not readily overlooked.

A type of pneumonia called interstitial is seldom recognized clinically, except by inference. The early symptoms suggest the onset of lobar pneumonia. Examination of the patient discloses signs of fluid in the pleural cavity. These are the cases of primary empyema (so called). The characteristic feature is the rapid formation of the pus. A patient having only symptoms of an infection may, within six or eight hours, develop symptoms of intrathoracic pressure, with signs indicating a pleural cavity full of fluid. To one who has not watched such cases and seen the pus return after aspiration and fill a cavity overnight the peculiar feature of this infection is scarcely creditable. Interstitial pneumonia received some attention in cantonment hospitals during last winter. Kaufmann's² classical description covers the essential features of the pathology.

Diagnosis. The diagnosis of bronchopneumonia cannot invariably be arrived at from the physical signs alone. Those somewhat unusual cases of multiple, discrete foci give none of the typical signs of consolidation, and these could not be expected when the foci are no larger than peas. The picture presented by the radiogram is misleading to the unwary and is not infrequently regarded as military tuberculosis, which, indeed, it may resemble post mortem. The signs in these cases are those we customarily associate with bronchitis. There is, however, something more than rales to be heard; a variability in the intensity of the breath sounds in contiguous areas is peculiar and arrests attention if one be on the lookout for this phenomenon. However, in some cases the diagnosis must be inferred, the temperature being too persistent and an increased respiratory rate speaking against bronchitis. When possible to procure one, stereoscopic radiograms may aid in confirming the diagnosis.

Even relatively small areas of consolidation are detectable by a skilled technic. Unless the area involved be near the costal pleura, however, impairment of resonance and frank change in breath sounds will not be notable. The change in the character of the signs over suspected spots at different examinations is in itself significant. The fleeting and migratory character of the consolidations in lobular pneumonia is peculiar to the disease. The earliest definite sign, and the one of most help when other signs are equivocal, is the change in the whispered voice which is transmitted to the ear with an abnormal clearness and with a slight nasal quality. Transmission of the whispered voice is a helpful sign in the recognition of changes of density in the lung substance and is often the earliest sign in all types of pneumonia. Because this sign is so frequently neglected some amplification is appropriate. A confusion exists in the minds

² Speziellen Path. Anat., 1911, 261.

of many concerning the significance of variations in the transmission of sound vibrations, because the attention is given only to intensity or loudness of sound, whereas variations in quality of the sound or in its pitch are even more significant and the examiner must take pains to keep these several features entirely distinct. For example, sounds of low pitch are better transmitted to the chest wall through normal lung than are equally intense sounds of higher pitch. With a solid lung, on the other hand, vibrations of all pitch are equally well transmitted. In bronchopneumonia small areas of consolidated lung substance are surrounded by air-containing lung, and this latter appears to "dampen" some vibrations more than others; the overtones being least affected are transmitted to the chest wall. Another factor is the bone conduction of the spoken voice which enters as a confusing element in auscultation; this confusion is less

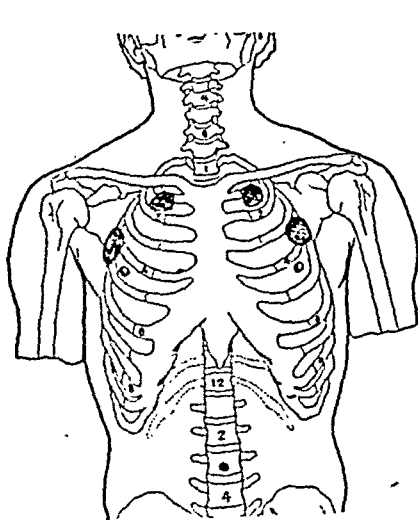


FIG. 1

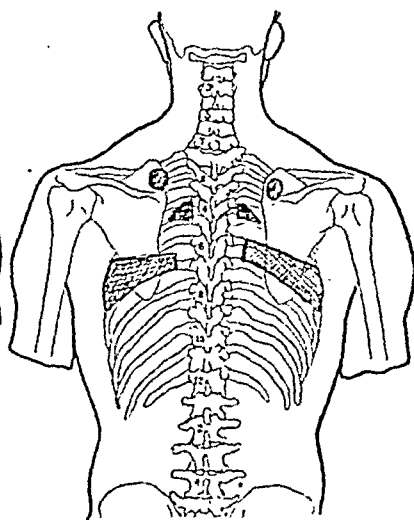


FIG. 2

pronounced or negligible in whispered pectoriloquy. Flint called attention to elevation of pitch as a sign of consolidation and the nonessential factor of mere intensity of sound.³ It has repeatedly happened that whispered pectoriloquy was the only definite physical sign over small areas where consolidation was demonstrated by radiogram. Where the consolidation is of considerable size there is usually no difficulty in its recognition.

Bronchopneumonia, alike with lobar pneumonia, shows a predilection for the lower lobes and is noted most frequently in certain areas which are illustrated in the charts (Figs. 1 and 2). The mild cases, infections of low virulence, may not come under observation until

³ See a clarifying analysis of these factors by Adams and Montgomery, *Jour. Am. Med. Assn.*, 1919, lxxii, 987.

convalescence, and then the question of tuberculous infection is often uppermost. The site of the consolidation is of help in decision on this question, as tuberculous infections are not usually located in the bases of the lungs. The confusion of tuberculosis with delayed resolution of bronchopneumonia has been the subject of frequent remark by those especially interested in tuberculosis,⁴ and it will be recalled that the mistake was made so often in the army that it became necessary to restrict the diagnosis of tuberculosis to those cases with tubercle bacilli in the sputum. Comment on this significant fact is hardly necessary.

Complications in lobular pneumonia, according to my case records, are more common than with lobar pneumonia. Except in young children, otitis media can hardly be overlooked, but empyema and pulmonary abscess very frequently escape recognition. Some experience outside of medical centers has convinced me that the so-called "septic pneumonia" of rural districts is usually empyema. Two erroneous notions are primarily responsible for the failures of recognition of empyema: (1) the idea that empyema is accompanied by a definite type of temperature curve, and (2) the idea that empyema gives rise to definite, characteristic physical signs. Both of these conceptions are narrow and misleading. The diurnal variation of temperature which is expected is so frequently absent that the type of fever is of little aid in diagnosis. While it may be true that with empyema following lobar pneumonia the temperature comes to normal in the majority of cases and then again becomes elevated, this fact is seldom applicable to the fever of empyema following lobular pneumonia. The accompanying charts (1 and 2) illustrate the diversity of febrile reactions. In some cases a sharp rise in the pulse-rate is more significant than the temperature curve.

Occasionally small pleural abscesses become so walled off that there is slight or no fever, the patient remaining an invalid for indefinite periods. In one case of this type the history pointed to an ambulatory pneumonia fourteen months before as the cause of the abscess.

The physical signs of empyema are so variable and departures from the text-book descriptions so frequent that it is necessary to hold broad and elastic conceptions and abandon the definite picture customarily held. Some cases undoubtedly show characteristic changes on examination, such as a dull or flat percussion note, impaired or absent vocal fremitus, with distant suppressed breath sounds approaching a bronchial type; but again it must be recognized that exceptions are exceedingly common.

Pleural abscesses tend to be sacculated and the surrounding lung tissue may be either consolidated in part or markedly emphysematous. The variations in these structural changes in the lung paren-

⁴ Ash; Jour. Am. Med. Assn., January 2, 1915, lxiv, 11. McCrae and Funk, *idem*, July 19, 1919, lxxiii, 3.

chyma give origin to variations in physical signs; moreover, there seems to be a tendency for the focus of suppuration to take place first in a fissure between the lobes, with subsequent extension.

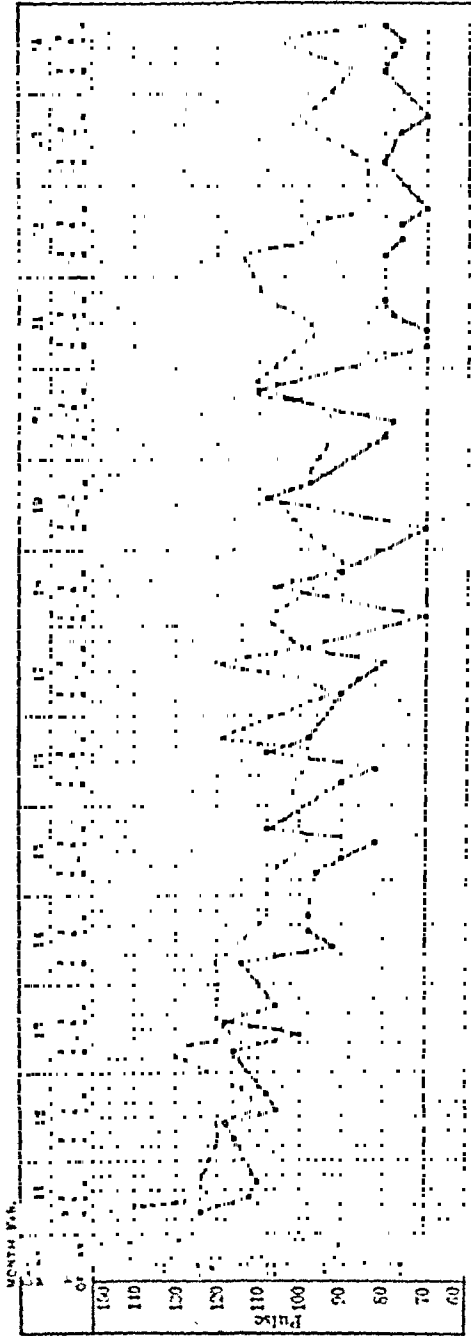


CHART I.—Typical bronchopneumonia. Empyema demonstrated on 10th.

When firm adhesions have been formed between the costal and parietal pleura there may be a thin lappet of air-containing lung between the ribs and pus. Postmortem examinations have revealed conditions of this sort and helped in an understanding of the marked variation in the peculiar physical signs. The fact should be emphasized that in many cases it is absolutely impossible to determine, by physical signs alone, whether the diseased condition in the lung is consolidation, fluid or both. The diagnosis, under these circumstances, can be determined only by exploratory puncture. Modified skodaic resonance in areas of the lung adjacent to collections of liquid has been to me of great assistance in diagnosis. The note elicited by percussion in the upper axillæ or over the lower portion

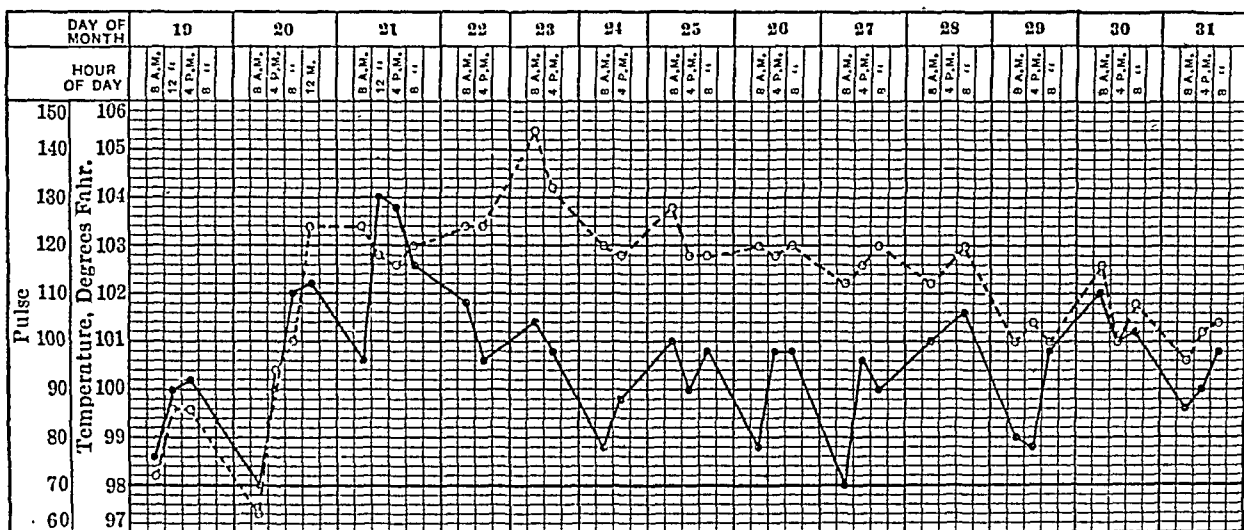


CHART II.—F. W., aged twenty-eight years. Case of Dr. Payne. Interstitial pneumonia (?). Empyema. On 20th, signs of slight bronchitis only; pain in the left chest. On 21st, at 10.30 A.M., careful examination failed to disclose suspected pneumonia; at 3.30 P.M. of same day, dullness, impaired fremitus and distant vesicular breath sounds over the left base posteriorly. Exploratory puncture. Pus. Infection due to *Streptococcus hemolyticus*. Aspirations; operation on 30th.

of the upper lobe overlying or adjacent to fluid has a high-pitched tympanitic quality approaching the amphoric. This peculiar alteration in the percussion note I have only seldom detected in a like degree over areas of lung adjacent to consolidation. This skodaic resonance is so marked that in several instances examiners of skill have mistaken the underlying condition for cavity. To me this sign is more significant than impairment of resonance or even flatness in the percussion note over fluid. Fluid is not always detected, even when present, because the exploring needle is not introduced in the proper area and sometimes, indeed, the fluid cannot be found. An interesting example of this occurred in my service at Camp Meade Base Hospital. A patient developed, following pneumonia, typical signs of fluid in the pleural cavity. There was no dissent concerning

the diagnosis. The chest was needled by the ward surgeon with no success, by the assistant chiefs, the chief, and later by others on the staff. No interspace from spine to sternum in the suspected area

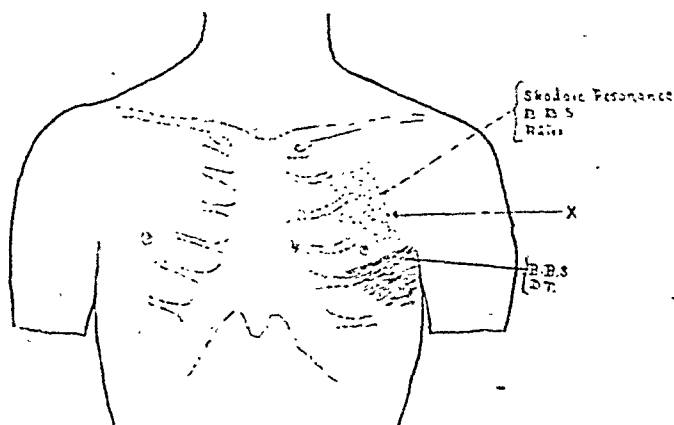


FIG. 3.—Atypical signs in empyema. Anterior view: Shading, impaired resonance to flatness; A, hyperresonant; B, skodaic resonance to amphoric; D.T., "dry tap," i. e., fluid not found; X, fluid determined by puncture; B.B.S., bronchial breath sounds; R, rales, crepitant and subcrepitant.

escaped. The patient finally improved, the fever disappeared but the signs persisted. One day while sitting on the ward porch he had an

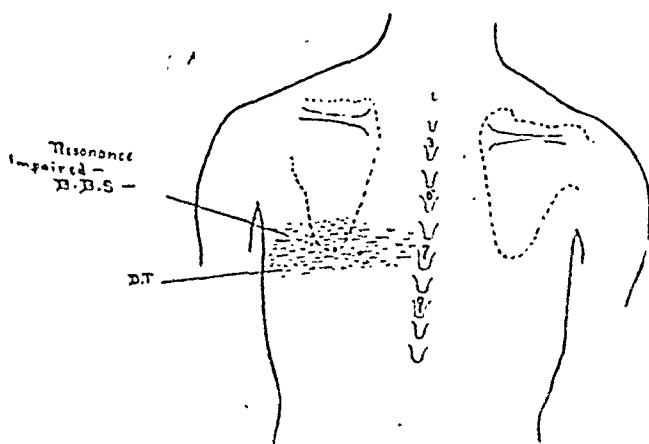


FIG. 4.—Atypical signs in empyema. Posterior view of same case as shown in Fig. 3: Shading, impaired resonance to flatness; A, hyperresonant; B, skodaic resonance to amphoric; D.T., "dry tap," i. e., fluid not found; X, fluid determined by puncture; B.B.S., bronchial breath sounds; R, rales, crepitant and subcrepitant.

attack of severe coughing and began to bring up pus. Some was lost, but the nurse saved over a pint as evidence of the correctness of the diagnosis. The patient made a perfect recovery. I know of

no guide that is infallible; certainly physical signs are often enough misleading. In many cases, however, there can be detected, by

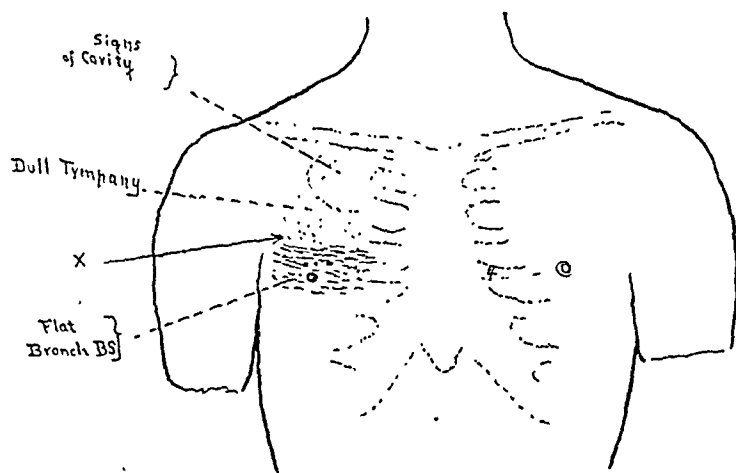


FIG. 5.—Atypical signs in empyema. Anterior view; Shading, impaired resonance to flatness; *A*, hyperresonant; *B*, skodaic resonance to amphoric; *D.T.*, "dry tap," *i. e.*, fluid not found; *X*, fluid determined by puncture; *B.B.S.*, bronchial breath sounds; *R*, rales, crepitant and subcrepitant.

careful examination, some spot where pressure produces acute pain, and I have found that this area of hyperesthesia is the most promising site for exploration. The accompanying illustrations

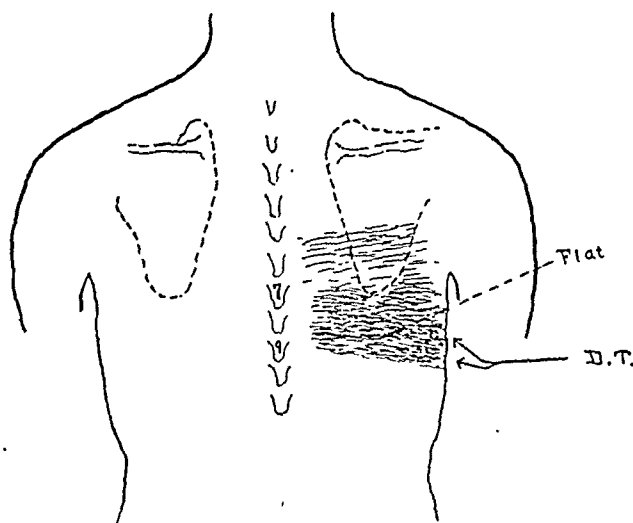


FIG. 6.—Atypical signs in empyema. Posterior view of same patient as shown in Fig. 5: Shading, impaired resonance to flatness; *A*, hyperresonant; *B*, skodaic resonance to amphoric; *D.T.*, "dry tap," *i. e.*, fluid not found; *X*, fluid determined by puncture; *B.B.S.*, bronchial breath sounds; *R*, rales, crepitant and subcrepitant.

(Figs. 3, 4, 5 and 6) are of some interest, not only in depicting the peculiarity of physical signs in some cases of empyema but also in

showing that several unsuccessful explorations do not prove the absence of fluid. There is no explanation for the fact that the area of maximum flatness is needled so often with no result, and a proximate hyperresonant area is shown by puncture to overlie fluid. It must also be borne in mind that there may be more than one separate collection of pus.

Finally, in the diagnosis of empyema I cannot too strongly disagree with the teaching that there is always a displacement of neighboring viscera, *i. e.*, heart or liver. Abscesses in the pleura of considerable size can develop in a lung bound down by adhesions without appreciable displacement of neighboring organs. On the other hand, marked emphysema in the uninvolved lung may produce displacement of the heart toward the diseased side. This fact has been noted at autopsy.

In the treatment of these cases of empyema the conception no longer holds that diagnosis should be followed by immediate thoracotomy. Early operation, before firm adhesions have been formed surrounding the suppuration, leads to pneumothorax and infection of the whole pleural cavity. The mortality under these circumstances is known to be high. Repeated aspirations, on the other hand, allow time for adhesions to form; the patient during this interval recovers to some extent from the severity of the infection, and, when finally subjected to operation, not only is the local condition in the lung walled off and better suited for drainage, but the patient's general resistance is higher and he is better able to withstand the shock of operation. A small percentage (in my experience about six) of the cases of empyema will recover following repeated aspiration alone and never require surgery.

The question arises at this juncture, For how long a period should aspirations be continued: in other words, for how long can operation be postponed? The answer is not as difficult as it might seem. So long as the patient continues to improve operation can be deferred. The criteria for improvement are better appetite and sleep, a lower fever and pulse-rate and evidences of diminished infection, such as less sweating and improvement in the patient's sense of well-being and strength. On the average this period of improvement will continue for about ten days. With a few the period is prolonged into convalescence. In some cases the reason for final operation is that the pus becomes so thick that drainage cannot be effected through a large needle. With others the indication for operation is an increase in the temperature, a failing appetite and the general appearance of the patient.

Of the relation of pulmonary abscess to bronchopneumonia we have but little knowledge. In three of my cases of abscess of the lung the history indicated very strongly a beginning of the affection in bronchial pneumonia. In one of these cases this is more than

probable, since the pneumonia developed after operation, the so-called ether pneumonia. The reason for mentioning pulmonary abscess in the present connection is that occasionally pulmonary abscess can be cured by artificial pneumothorax. This procedure is indicated, however, only when there are no pleural adhesions, since, of course, with such adhesions the desired collapse of the lung cannot be produced. In two cases, where the abscess was in the mesial portion of one of the lower lobes, artificial pneumothorax resulted in an abatement of the symptoms and the last case treated is well up to the present time, a period of about two years since treatment was discontinued. When the abscess is near the pleura, as unfortunately it frequently is, adhesions usually occur and the only cure under these circumstances is lobectomy.

The most common of the sequelæ of bronchopneumonia, alike with lobar pneumonia, relates to the heart. Slight involvement of the myocardium, as manifested by breathlessness on exertion, is so common, following all types of pneumonia, that it is to be regarded as one of the incidents of convalescence. With not a few individuals, however, this symptom is prolonged for a number of months. Affections such as described are by no means confined to the elderly or to those who have some preëxistent cardiac disorder, but are manifested not infrequently in robust young men. The physical signs are seldom clear cut, and of themselves would hardly disclose the nature of the disorder. The heart sounds may not be as clear as they should be and occasionally a systolic murmur can be heard at the apex. But these signs can be noted in a considerable number of apparently healthy persons. The significant fact is the symptoms of circulatory embarrassment coming on after an acute infection. From a therapeutic point of view it is important first to recognize the nature of the disorder, with a view to protecting the patient against premature severe physical exertion. Time alone corrects the great majority of these disabilities. In addition, well-supervised graduated exercises have a distinct use, as was demonstrated on such a large scale in the military convalescent camps.

In conclusion, it is desirable to emphasize that bronchopneumonia is a common affection in young, robust individuals, and that, on account of the physical signs, the disease may, in mild cases, be easily overlooked. The treacherous character of bronchopneumonia and the seriousness of its complications and sequelæ indicate the importance of early recognition and adequate protective care.

EXPERIMENTAL STUDIES IN DIABETES:

SERIES II. THE INTERNAL PANCREATIC FUNCTION IN RELATION
TO BODY MASS AND METABOLISM.

II. CHANGES IN ASSIMILATION BY ALTERATIONS OF BODY MASS.

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THE preceding paper¹ was a study of the alterations of assimilation produced by changing the mass of the pancreas. The present one deals with the alterations of assimilation produced by changing the body mass. Attention was first given to these relations in obese dogs.

I. PANCREAS AND BODY MASS RELATIONS IN OBESE DOGS.

The following conclusions were drawn (Table I):

1. No anatomic differences were found between different ages or different types of obesity. At one extreme are young animals which are fat apparently for the sole reason that they eat enormously and are very lazy. At the other extreme are a type well known to those who handle many dogs, namely, animals in advanced senility, toothless or with teeth worn to the gums, excessively obese and sluggish, generally either surly or stupid, and consuming sometimes a large and sometimes a surprisingly small quantity of food. Both types of animals in the above series were free from either gross or microscopic changes in the pancreas; in particular, from either fibrous or fatty invasion or island changes. If it is permissible to apply these observations to human pathology, it may be concluded that such changes in the pancreas are a distinct abnormality and not naturally attendant upon either obesity or senility.

2. Even with the extreme degrees of obesity here represented, the ratios of pancreas weight to body weight fell within the normal limits shown in Table II, Paper 1 of Series I.² This is not because this ratio does not change when an animal becomes fat, but merely because the variations in the ratio in different normal dogs are so wide. It is therefore not possible to demonstrate an abnormal susceptibility to diabetes in obesity on the basis of a reduced mass of pancreas in proportion to the body mass.

¹ Allen, F. M.: *AM. JOUR. MED. SC.*, 1920, clx, 781.

² Allen, F. M.: *Jour. Exp. Med.*, 1920, xxxi, 366.

3. It was mentioned in the preceding paper that alterations of body weight, apart from starvation or cachexia, do not change the glucose tolerance of normal dogs. Similar tests upon obese animals have shown no departure from the normal assimilation, as far as interpretation was possible. Protocols are omitted because there can be no claim to accuracy in comparisons, since reckoning dosage on the obese weight is obviously unfair and only guesses could be made of the normal weight. Nevertheless any serious reduction of tolerance would have been evident, and the conclusion is justified that neither obesity nor senility *per se* involves any demonstrable lowering of glucose assimilation.

TABLE I.—PANCREAS AND BODY MASS RELATIONS IN OBESE DOGS.

No.	Body weight, kgm.	Weight, total pancreas, gm.	Grams of pancreas per kgm. body weight.	Weight of remnant, gm.	Size of fraction.	Diabetes.	Remarks.
1	6.5	17.6	2.71	1.50	$\frac{1}{11}-\frac{1}{12}$	Senile, excessively obese; cachexia without glycosuria.
2	7.0	14.7	2.10				
3	7.2	12.2	1.69	1.30			
4	8.9	19.3	2.17	Age three years.
5	9.3	22.8	2.45	2.90	Senile.
6	9.7	22.0	2.27	Old.
7	12.0	26.3	2.19	3.40	$\frac{1}{8}$	Mild with removal of 0.85 gm. additional in 3 subsequent operations	Obese young dog.
8	14.3	30.8	2.15	3.25	Moderately old and fat.
9	14.8	31.3	2.11				
10	14.9	32.5	2.18	1.65	$\frac{1}{6}$	Gravis	Age four years.
11	16.4	35.2	2.42	5.60	$\frac{1}{6}-\frac{1}{7}$	Not excessively obese.
12	17.0	31.6	1.86	4.60	$\frac{1}{7}$	Levis	Age three years.
13	18.6	22.9	1.61	4.25	$\frac{1}{5}-\frac{1}{6}$	Levis	
14	18.6	39.2	2.11	Age six years.
15	19.0	36.3	1.86				
16	19.2	31.0	1.61				
17	19.5	36.3	1.81	1.20	$\frac{1}{30}$	Gravis	
18	20.0	28.4	1.42	5.50	$\frac{1}{5}$	Death in three days.
19	20.5	41.0	2.00	12.00	$\frac{1}{3}-\frac{1}{4}$	Age four years; normal wt. estimated at 13 kilos.
20	20.9	37.7	1.80	2.90	Old.
21	22.8	33.4	1.46	1.30	$\frac{1}{20}$	No glycosuria; death within three days.
22	22.8	41.1	1.80	7.50	$\frac{1}{5}-\frac{1}{6}$	None	Age six or seven years.
23	24.3	42.9	1.76	6.10	"Rather old."
24	25.0	51.2	2.04	6.50	$\frac{1}{8}$	Gravis	Fat but not pathologically obese; glycosuria in spite of prostration.
25	28.5	46.3	1.62	Moderately obese.
26	32.4	61.3	1.89	12.4	$\frac{1}{5}$	Transitory with prolonged glucose diet.	

4. The types of obese dogs mentioned react differently to partial pancreatectomy. The younger ones generally withstand the operation well. The senile ones very commonly die within one to three days, presumably of the pancreatic intoxication which is called "fat necrosis" from one of its minor accompaniments. The deaths are not due to ordinary shock, because such animals safely undergo control operations involving more trauma and exposure of viscera and sometimes survive total longer than partial pancreatectomy. Senility is not always a factor, because a few younger dogs with a type of obesity apparently due to endocrine disorder likewise die abruptly after such operations, while some of the old obese kind which retain greater liveliness survive. Injections of pancreas extract have not conferred immunity, but it is sometimes possible to immunize the animals by successive operations, removing only a very small piece of pancreas the first time. The results are not very satisfactory, because the dogs generally either lose their obesity or die before the series of operations is complete.

5. The main question under consideration was whether obese dogs would for any reason be more susceptible to diabetes than normal dogs. The results with dogs Nos. 12, 13, 24 and 26 in Table I suggest that this may be the case. Diabetes was not produced in any of these animals with larger pancreas remnants than in some of the normal dogs of Paper 1, Series I, but the proportion of positive to negative results with remnants of this size is much higher in the obese series. This latter series is, however, so short that no positive conclusion is warranted.

II. ALTERATIONS OF BODY WEIGHT IN THE SAME ANIMAL.

It was concluded in Series I that various influences can be most accurately judged by applying them to partially depancreatized animals and observing the individual alterations of assimilation. One important procedure would be to depancreatize a dog just short of diabetes and then determine whether the most extreme fattening could actually bring on diabetes, *i. e.*, whether obesity can ever be a genuine cause of diabetes to an extent equal to the removal of a small fraction of a gram of pancreatic tissue. This point was not covered by this investigation because of the practical difficulties. The method actually used consisted in taking diabetic dogs free from symptoms on fixed diets and studying the changes of assimilation produced by alterations of the nutritive level. Changes of tolerance in inverse relation to the body weight were mentioned incidentally in Series I, without strict proof of the causal character of the relation. The present experiments were

designed to furnish such proof, on different diets, but particularly including changes of weight produced entirely by changes of the non-sugar-forming element of the diet, namely, fat. The difficulties of carrying through such long experiments successfully were referred to in Series I.

Dog B2-10.

Female, mongrel, white, aged nine months, good condition; weight, 7 kilos.

November 18, 1913, removal of pancreatic tissue weighing 16 gm. Remnant about main duct estimated at 1.8 gm. ($\frac{1}{10}$). There was glycosuria as high as 4 per cent., which with onset of distemper diminished in spite of bread and glucose feeding and disappeared December 1. Weight was rapidly lost through anorexia and diarrhea. The lowest level reached was 4.4 kilos. With gradual recovery from the distemper weight was gained on plain bread and soup diet, and glycosuria ensued when the level of 5.1 kilos was attained on February 19. The diet was then changed to beef-lung *ad libitum*, glycosuria remained absent, and in subcutaneous tolerance tests in March and April there were traces of glycosuria with 2 gm. glucose per kilo (reckoned on the original 7 kilos weight), but none with 1.8 gm. or less. The weight, which was slowly increasing, was 6 to 6.3 kilos during this time. By July 29 the dog was obese at a weight of 10.4 kilos, and on this date glycosuria appeared and persisted during the following week until checked by fasting and reduced diet.

Dog C3-20.

Male, mongrel, brown, aged six to eight years; fair nutrition; weight, 24 kilos.

June 24, 1915, four-fifths of the pancreas was removed and additional tissue on July 16 and 30. Glycosuria was present on glucose and bread feeding, but ceased, and on plain bread diet on August 15 the plasma sugar rose only to 0.143 per cent. and was 0.088 per cent. the following morning. August 16 an additional 0.6 gm. of pancreatic tissue was removed and the diet was changed to beef-lung *ad libitum*. The weight at this time had fallen to 21.3 kgm. On August 25 the plasma sugar during digestion rose to 0.154 per cent., *i. e.*, higher on protein diet than on carbohydrate prior to the last operation. On September 29, at a body weight of 24.8 kilos, the plasma sugar was 0.077 per cent. immediately before feeding, 0.078 per cent. immediately after feeding and 0.161 per cent. five hours later. October 23, at a body weight of 25.8 kilos, glycosuria of 1.1 per cent. suddenly appeared and ceased

only with two days of fasting. The former diet was then resumed and on November 1 sugar suddenly reappeared in the urine in 2.4 per cent. concentration.

Dog B2-52.

Female, bull terrier mongrel, brindle, aged five or six years; excellent condition; weight, 12.8 kilos. April 24, 1914, seven-eighths of the pancreas was removed, and glycosuria proving transitory, half the remnant was removed on May 18. The weight meanwhile had fallen to 9.3 kgm. Glycosuria was immediately checked by fasting and a diet carefully built up, beginning with 50 gm. beef-lung and 50 gm. suet, and increasing so that by June 15 the dog was eating 1000 to 1200 gm. lung without glycosuria. July 30, glycosuria began with 0.53 per cent. sugar in 507 c.c. urine, followed by 1.6 per cent. in 836 c.c. the next day, at a body weight of 11.4 kgm. Continuous fasting to August 12 then reduced the weight to 9.3 kgm. as before, and the diet was built up as before. The dog would no longer eat the full quantity of lung, and it was necessary to introduce 50 to 100 gm. lard for fattening. On the lard and quantities of lung below 1000 gm., glycosuria remained absent until November 25. Then at a body weight of 12.5 kilos glycosuria of 0.4 to 2 per cent. was present for four days, ceased with a single fast-day, remained absent on the regular diet for a week, then on the same diet was present for two weeks, the weight during this time ranging as high as 14.3 kgm. and the animal appearing in splendid condition. It was then found impossible to stop the glycosuria, and after two weeks of fasting the dog died of acidosis.

Dog B2-57.

Female, mongrel, yellow, aged five years, good condition; weight, 11 kilos. Fasting from May 4 to May 21, 1914, reduced the weight to 8.7 kilos. On the latter date 19.6 gm. of pancreatic tissue was removed, leaving a remnant estimated at 2 gm. ($\frac{1}{11}$). Glycosuria remained absent while the diet was gradually built up.

June 14, at a body weight of 7.5 kgm., a diet of 1200 gm. beef-lung was begun, and the dog ate this quantity daily without glycosuria until July 30. On this date there was 0.38 per cent. glucose in 390 c.c. urine and the next day 1.7 per cent. in 635 c.c., the body weight being 10.4 kilos.

Fasting was then continued to August 12, reducing the weight to 8.1 kilos. The diet was then built up gradually to 500 gm. lung on August 22, the weight being 7.7 kgm. on that date. The dog

remained without glycosuria on this diet to September 14, when the weight had declined to 7.4 kilos.

September 14, 50 gm. lard was added to this diet, increased on October 5 to 100 gm. October 20, at a weight of 10.8 kgm., lard was stopped because the dog was tired of it, and the lung was increased to 1000 gm. daily. The dog was on this diet to November 13 and gained weight to 11.4 kilos.

November 13, 50 gm. lard was added, increased on November 18 to 100 gm. The lard was now eaten and considerable of the lung was left uneaten. December 24 the weight had risen to 16.3 kilos, which was marked obesity. Glycosuria then began and continued (0.3 to 4.2 per cent.) on the same diet to January 4.

Fasting then stopped the glycosuria in two days, but was continued five days, reducing the weight to 14.25 kilos. Lung feeding was then begun cautiously, with 100 gm. the first day to 500 gm. on January 14, when glycosuria of 0.18 per cent. appeared in 186 c.c. urine. This increased to 1.4 per cent. in 240 c.c. urine and ceased with a single fast day, but successive attempts at feeding now caused glycosuria more easily, until on January 31 it resulted from only 150 gm. lung. Fasting then proved unable to stop the glycosuria, and the dog died March 1, still showing 0.9 per cent. sugar in 1295 c.c. urine, with a body weight of 6.8 kilos.

Dog B2-79.

Male, bull terrier mongrel, brindle, aged four or five years, medium nutrition; weight, 15 kilos. November 10, 1914, removal of pancreatic tissue weighing 32.2 gm. Remnant about main duct estimated at 4.7 gm. ($\frac{1}{8}$).

Glycosuria following operation on bread diet ceased on a diet of 800 gm. beef-lung. From February 16 to April 2, 1915, the diet was 1000 gm. of lung, but the dog was cachectic and lost weight down to 11.2 kilos. The diet was then changed to bread and soup *ad libitum*, with benefit to the general health, and glycosuria remained absent to April 7, when the diet of 1 kilo of lung was resumed. The dog was anemic at this time, with a red cell count of 2,700,000, but began then to improve in digestion and health, gradually regained the original weight and vigor and was used for exercise and other incidental experiments, which did not lower the tolerance. The exercise in fact seemed to prevent glycosuria, as described in the following paper.

In September glycosuria could no longer be restrained on the diet of 1 kilo of lung but was absent on a diet of 500 gm. lung and 500 gm. suet. The dog was greedy for the suet, and by October

3 was obese at a weight of 17 kilos. Glycosuria of 0.77 to 1.5 per cent. was then present October 3 to 6.

October 7 to November 8 the dog was fed nothing but suet or lard. At first these were eaten abundantly, but at the end both appetite and digestion were spoiled. The weight diminished to 13.5 kilos. Glycosuria ceased the first day and blood sugar analyses reported elsewhere showed that the fat had no tendency to create hyperglycemia. Nevertheless, when a diet of 500 gm. lung was begun on November 9, glycosuria (0.84 per cent. in 323 c.c.) appeared on November 11, i. e., there was not the rise of tolerance which occurs with such a fall of weight under other conditions.

Glycosuria was then kept absent with reduction of protein, while the weight was kept slightly below and above 14 kilos by the use of as much fat as the dog would take. Beginning December 7, the diet was 300 gm. lung and 200 gm. suet. Glycosuria was absent until January 2.

January 2, 1916, there was glycosuria of 1.5 per cent. in 194 c.c. urine, ceasing with a single fast day. Again, the protein was diminished, making the diet 200 gm. lung and 200 gm. suet. The weight was 14.2 kilos. It was possible to increase the suet to 300 gm. and then to 400 gm., so that by January 30 the dog weighed 14.9 kilos. Glycosuria then returned; no fasting was employed to check it, and the dog was allowed to pass on into hopeless diabetes.

Dog B2-80.

The earlier history of this animal was given in Paper 2 of Series I.³ The carbohydrate diet and glycosuria in April and early May, 1915, were carried to such a point that the dog could not tolerate 1000 gm. of lung at a weight of 15.5 kilos. Repeated trials of this diet, interspersed with fast days, reduced the weight by June 2 to 13.2 kilos. The kilo of lung was then tolerated until June 9, when there was 0.17 per cent. sugar in 681 c.c. urine, followed by 0.72 per cent. in 607 c.c. the next day.

The glycosuria ceased with a single fast day and the diet was changed to 500 gm. lung and 300 gm. suet. Weight was gained very rapidly and on June 21 there was a return of glycosuria at a weight of 17 kilos.

This glycosuria required two days of fasting to stop and the protein was then further reduced, making the diet 250 gm. lung and 300 gm. suet. The weight continued to increase and the dog had the appearance of splendid health. The photograph at the end of Series I⁴ was taken July 2, at a weight of 18.2 kilos. On July

³ Allen, F. M.: Jour. Exp. Med., 1920, xxxi, p. 383.

⁴ Ibid., Fig. 7, Plate 66, following page 608.

10 there was a sudden appearance of 1.4 per cent. sugar in 605 c.c. urine.

After two fast days to stop the glycosuria the diet of 250 gm. lung and 300 gm. suet was resumed and the dog was used for exercise experiments, as described in the following paper. Increasing glycosuria and acidosis led to death in coma on August 14.

Dog B2-01.

Female, large fox-terrier mongrel, aged two years, good condition; weight, 14 kilos. This dog was received October 25, 1913, and used first for successive removals of pancreatic tissue and tests of the tolerance as described in the preceding paper. Diabetes was finally produced by the removal of 0.8 gm. pancreatic tissue on August 31, 1916. The following record contains some details already referred to in the preceding paper and in Series I.⁵

Summary. Beginning September 1, 1916, at a weight of 11.4 kgm., the dog was free from glycosuria not only on unlimited bread diet but even with addition of 300 gm. glucose. With continuance of plain bread feeding and a slight gain of weight to 11.7 kgm. the tolerance by November 15 had fallen so that a considerable percentage of glycosuria resulted from giving 56 gm. glucose by stomach tube. The fall in tolerance was further indicated by the repeated glycosuria on bread diet up to December 25; sugar would appear and be checked by fasting; a few days later it would reappear and be checked again; and notwithstanding the slight loss of weight, there was the usual gradual decline of tolerance on this program, as indicated by the two days of fasting necessary, December 26 to 27, in contrast to the single days which previously sufficed.

From December 28, 1916, the only food given was a quantity of bread and soup mixture measured in a cup so as to be roughly uniform though not weighed, and representing a slight under-nutrition diet, so that there was a gradual fall in weight to 9 kgm. on February 22, 1917. The tables show that at this low weight the blood sugar was normal both before feeding and during digestion of this diet, and the assimilation as judged by a test-meal on February 23 was notably higher than at the higher weight in the preceding November.

Beginning February 24, 100 gm. beef-lung and 100 gm. suet were given daily in addition to the above cup of bread and soup, so as to fatten the dog. The weight thus rose to 14.5 kgm. on June 8 and to 15.25 kgm. on June 12. Glycosuria occurred on June 8, was absent the next day and was continuous June 10 to 12.

⁵ Allen, F. M.: Jour. Exper. Med., 1920, pp. 396, 564, 570, 600.

TABLE II.—DOG B2-01.

Date.	Weight, kgm.	Diet.	Remarks.
1916.			
Sept. 1-4	11.4	Bread and soup <i>ad libitum</i>	No glycosuria.
5	11.5	Same, with 100 gm. glucose	No glycosuria.
6	11.5	Same, with 200 gm. glucose	No glycosuria.
7	11.5	Same, with 300 gm. glucose	No glycosuria.
8-Nov.			
14	11.5-11.7	Bread and soup <i>ad libitum</i>	No glycosuria.
Nov. 15	11.7	56 gm. Merek glucose in 30 per cent. solution by stomach tube (4 gm. per kgm. on 14 kgm. weight; no other food)	Before feeding, sugar neg.; two hours after, 18 c.c. urine, glucose 6.28 per cent.; five and one-half hours after, 38 c.c. urine, glucose 4.64 per cent.
16-30	11.6-11.1	Bread and soup <i>ad libitum</i>	No glycosuria except with tests (see below).
Dec. 1	11.1	Bread and soup <i>ad libitum</i>	1.5 per cent. sugar in 743 c.c. urine.
2	11.1	Bread and soup <i>ad libitum</i>	1.85 per cent. sugar in 581 c.c. urine.
3	Fasting	No glycosuria.
4-9	11.0	Bread and soup <i>ad libitum</i>	No glycosuria.
10	11.0	Bread and soup <i>ad libitum</i>	0.65 per cent. sugar in 1025 c.c. urine
11	11.0	250 gm. beef-lung	No glycosuria.
12-16	Bread and soup and 100 gm. lung	No glycosuria.
17	Bread and soup and 100 gm. lung	Slight glycosuria.
18-19	10.9	Bones only	No glycosuria.
20-24	Bread and soup and 100 gm. lung	Slight glycosuria.
25	11.2	Bread and soup and 100 gm. lung	0.6 per cent. sugar in 260 c.c. urine.
26-27	Fasting	Glycosuria ceased December 27.
Dec. 28, 1916-			
Feb. 22, 1917	Gradual fall to 9	Small cup of bread and soup daily	No glycosuria except with tests (see below); on February 19, plasma sugar before feeding 0.091 per cent. six hours after 0.133 per cent.
Feb. 24-June 7	Gradual rise to 14.5	Same cup of bread and soup, with 100 gm. lung and 150 gm. suet	No glycosuria except with tests (see below); on February 24, plasma sugar before feeding 0.102 per cent.
June 8	14.5	Same	0.9 per cent. sugar in 105 c.c. urine.
9	Same	No glycosuria.
10	Same	0.5 per cent. sugar in 160 c.c. urine.
11	Same	Slight glycosuria.
12	15.25	Same	0.4 per cent. sugar in 200 c.c. urine.
13-July 2	Gradual rise to 16.6	400 gm. lung and 200 gm. suet; no bread	No glycosuria except with tests (see below); on June 30, plasma sugar before feeding 0.147 per cent.
July 3-Nov.	Gradual fall to 9.6	450 gm. lung only	No glycosuria except with tests (see below).
Nov. 15	9.6	450 gm. lung and 50 gm. bread	Faint glycosuria.
16	450 gm. lung and 100 gm. bread	No glycosuria.
17	450 gm. lung and 200 gm. bread	Slight glycosuria.
18-Dec. 20	Gradual fall to 8	450 gm. lung only	No glycosuria except with tests (see below); on December 2, plasma sugar before feeding 0.044 per cent., four hours after 0.110 per cent.
Dec. 21-30	Gradual rise to 8.75	Lung and suet <i>ad libitum</i> , with small cup of bread and soup	No glycosuria; on December 27, plasma sugar before feeding 0.145 per cent., four hours after 0.164 per cent., seven hours after 0.147 per cent.
Dec. 31, 1917-	Gradual rise to 9.2	400 gm. lung and 50 gm. suet	No glycosuria; on January 15, plasma sugar before feeding 0.110 per cent., six hours after 0.130 per cent.; on February 4, plasma sugar before feeding 0.089 per cent.
Feb. 13, 1918			No glycosuria up to August, 1918.
After Feb. 13, 1918	Gradual rise	400 gm. lung and 100 gm. suet	

Beginning June 13 the diet consisted of 400 gm. lung and 200 gm. suet without carbohydrate. The weight rose to a maximum of 16.6 kgm., and the standard test-meal on June 26 showed a marked fall in assimilation. There was no other glycosuria, but evidently continuous hyperglycemia, as judged by the plasma sugar of 0.147 per cent. before feeding June 30.

Beginning July 3 the diet was only 450 gm. lung, in order to give low calories with as much protein as in the former diets. The weight thus fell gradually to 8 kgm. on December 20. On November 15, the addition of 50 gm. bread caused transitory glycosuria, as frequently results from carbohydrate after a carbohydrate-free diet; but there was none with 100 gm. bread the next day and only a slight reaction with 200 gm. on November 17. Rising assimilation was also indicated by the feeding tests of October 5, November 22 and December 18 (Table III). The hypoglycemia present on December 2 (and presumably the following days) corresponded to the emaciation and cachexia.

Beginning December 21 the diets were such as to produce gain in weight. Up to December 31, bread in quantities similar to those given a year previously was tolerated without glycosuria but with hyperglycemia. Bread was then omitted and the weight steadily rose on protein and fat.

Events prevented further accurate tests, but glycosuria was absent up to August, 1918, and the animal was fat at that time. Paper 5 of Series I⁶ gave the subsequent history up to death on October 15, 1919.

Remarks. 1. The first four tolerance tests (Table III) were arranged for judging the influence of the tests themselves. The quantity of 30 gm. glucose on November 20, 1916, was guessed at random, and proved smaller than desirable for a standard, as the glycosuria and hyperglycemia were too slight. A diet with 75 gm. glucose was given the next day and again on November 23. The test with 30 gm. glucose was repeated on November 27. As these closely spaced tests showed no significant differences between November 20 and 27 and November 21 and 23 it was concluded that the much less frequent subsequent tests could not be held responsible for any great changes of tolerance. This expectation was confirmed by the later observations of upward as well as downward fluctuations of the assimilation.

2. Attention may again be called to the close reproduction of typical human histories in the record of such an animal. Starting with an excellent physical condition and a very high tolerance it may be said that the occasional tolerance tests correspond to a

⁶ Jour. Exper. Med., 1920, xxxi, 600.

few violations of diet, but that otherwise almost continuous freedom from glycosuria was maintained; yet the course was downward to death from diabetes three years later. Such a clinical record might well be adduced as evidence of inherent and inevitable downward progress, yet the dietary causes in this animal are perfectly plain; and if the previous conclusion that such dogs are free from inherently progressive tendencies be well founded, it is evident that the diet was the sole cause in this instance.

TABLE III.—FEEDING TESTS. DOG B2-01.

Date.	Weight, kgm.	Plasma sugar, per cent.	Urine.			Remarks.
			Vol., c.c.	Glucose, per cent.	Total glu- cose, gm.	
Nov. 20, 1916	11.6	0.13	Fed 200 gm. bread, 100 gm. lung and 30 gm. glucose.
Before feeding	0.088	626	Neg.	
2 hours after	0.133	25	Very faint	
4 hours after	0.143	26	0.31	
6 hours after	0.164	18	0.27	Fed 200 gm. bread, 100 gm. lung and 75 gm. glucose.
Nov. 21, 1916	11.6	0.094	230	Neg.	0.42	
2 hours after	0.224	18	Faint	
4 hours after	0.256	30	0.68	
6 hours after	0.159	26	0.83	Same diet as Nov. 21.
Nov. 23, 1916	11.6	0.103	110	Neg.	0.33	
2 hours after	0.147	22	0.46	
4 hours after	0.182	22	0.38	
6 hours after	0.200	32	0.48	Same diet as Nov. 20.
Nov. 27, 1916	11.6	0.093	20	Neg.	0.20	
2 hours after	0.130	78	Very faint	
4 hours after	0.135	48	0.42	
6 hours after	0.095	27	Faint	Same diet as Nov. 21.
Feb. 23, 1917	9.0	0.135	46	Neg.	0.22	
2 hours after	0.128	17	0.42	
4 hours after	0.154	15	0.43	
6 hours after	0.178	21	0.43	Same diet as Nov. 21.
May 17	13.5	0.078	75	Neg.	4.79	
2 hours after	0.212	16	2.14	
4 hours after	0.244	34	5.18	
6 hours after	0.250	45	6.42	Same diet as Nov. 21.
June 26	16.6	0.132	7	Neg.	10.35	
2 hours after	0.345	32	2.99	
4 hours after	0.416	92	4.33	
6 hours after	0.370	110	4.93	Same diet as Nov. 21.
Oct. 5	11.5	0.133	21	Faint	1.69	
2 hours after	0.263	12	4.32	
4 hours after	0.250	15	4.23	
6 hours after	0.220	17	3.20	Same diet as Nov. 21.
Nov. 22	9.8	0.123	64	Neg.	4.85	
2 hours after	0.303	44	4.20	
4 hours after	0.256	27	5.61	
6 hours after	0.227	30	4.94	Same diet as Nov. 21.
Dec. 18	8.0	0.147	9	Neg.	0.21	
2 hours after	0.141	7	Faint	
4 hours after	0.175	11	0.78	
6 hours after	0.161	7	1.66	

3. This experiment was planned to include the question of the specific relation of carbohydrate to the pancreatic function, which was also raised in the experiment on Dog 428 in Paper 4 of Series I.⁷ The initial high carbohydrate diets undoubtedly reduced the assimilation more rapidly and powerfully than any other food, and at all stages carbohydrate obviously created the greatest tendency to glycosuria. On the other hand this experiment demonstrated (still more strongly than that on Dog 428), in the period December 28, 1916, to February 22, 1917, that with undernutrition a diabetic animal may live on chiefly carbohydrate diet without glycosuria and with normal blood sugar. In addition to refuting any exaggerated ideas concerning carbohydrate as a sole and specific poison in diabetes, this serves to check too great simplicity in the interpretation of the action of dietary restriction. To some extent it is doubtless true that the food carbohydrate and the body glycogen give rise to glycosuria, and it might be assumed that fasting and restricted diet merely reduce these two sources of urinary glucose. But it is a safe assumption that an animal undergoing slight gradual undernutrition on a bread diet has more glycogen than on a diet of 400 gm. beef-lung and 200 gm. suet (especially in view of the known influence of fat feeding in diminishing glycogen). The experiment then shows that the blood sugar may be lower and the tolerance higher under the former than under the latter conditions. In other words, diabetic glycosuria must be governed by something deeper than merely the quantity of carbohydrate available either in the food or in glycogen.

4. Attention was also paid to the protein ration, which was kept nearly enough equal so that fluctuations in the tolerance could not be attributed to it. Presumably the sugar which caused the hyperglycemia of June 30, 1917, and also that excreted in the active diabetes of 1919, was derived from protein, but the assimilation of this protein obviously varied widely with changes in body weight.

5. The changes in body weight were due essentially to fat feeding and fat deposit, and an influence of fat in connection with sugar metabolism and diabetes is thus demonstrated. The question whether the relation to the internal pancreatic function is direct or indirect is not answered by this experiment. On one hand is the predominant effect of carbohydrate in breaking down assimilation, as already mentioned; in the initial mild stage it is doubtful if the tolerance could ever have been broken down by fat or any non-carbohydrate diet. On the other hand, even in the later stage, carbohydrate was apparently assimilated well and harmlessly at a low level of nutrition, while overnutrition gradually brought

⁷ Jour. Exper. Med., 1920, xxxi, 581-586.

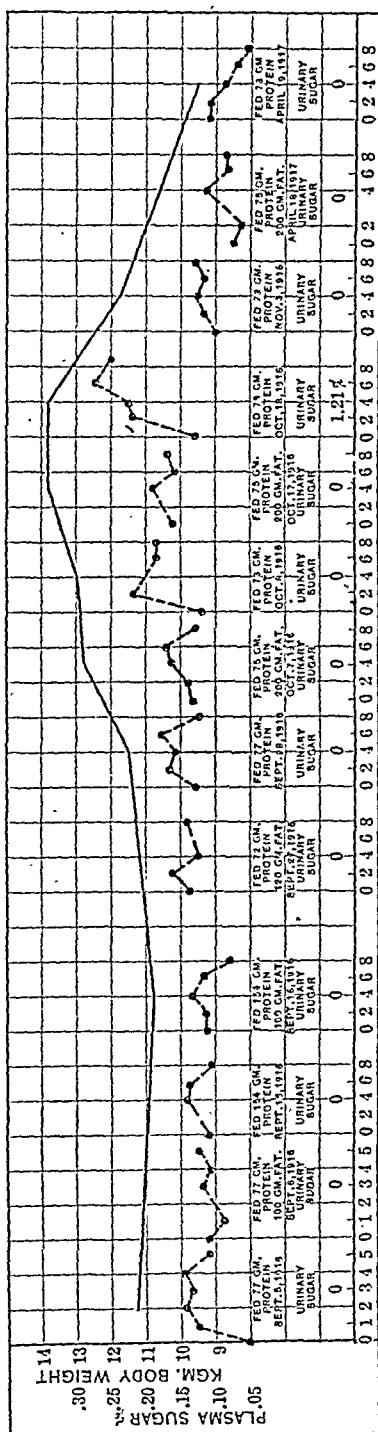


Chart of Tests Performed on Dog C3-86

on diabetes even in absence of preformed carbohydrate. In either case the overload of assimilation was manifested by glycosuria or hyperglycemia. There was no evidence of harm from either carbohydrate or gain of weight so long as these signs of overstrain of the carbohydrate side of metabolism were avoided; but forcing either the carbohydrate ration or the total nutrition beyond the limits set by these danger signals resulted in downward progress and finally hopeless diabetes.

Dog C3-86.

Female, mongrel, brown, aged two or three years, slightly obese; weight 15 kilos. April 28, 1916, removal of pancreatic tissue weighing 33 gm. Remnant about main duct estimated at 2.9 gm. ($\frac{1}{12}$ to $\frac{1}{13}$). Glycosuria was checked by fasting and undernutrition and the dog was kept in this border-line condition under careful tests until it was established that the assimilation limit amounted to about 800 gm. of beef-lung and that this tolerance showed no further tendency to change spontaneously. Beginning September 5 a series of tests were performed, most of which were previously published,⁸ and the two concluding ones are now added in the accompanying graphic chart.

The points of chief importance in this experiment are the following: (1) The protein of the diet was kept constant throughout and the changes of weight were produced solely by adding and withdrawing fat; (2) there was no indication of the conversion of fat into sugar—on the contrary, the plasma sugar curves were generally distinctly lower on the test days with protein plus fat than on the days with protein alone, probably because of slower absorption with the fat admixture; (3) under these conditions it was proved decisively that the assimilative power fell as the weight rose, and was restored even higher than the original level when the body weight was reduced below the original level.

III. ALTERATIONS IN BODY MASS IN THE FORM OF ACTIVE PROTOPLASM.

In the preceding paper has been described the phenomena resulting from reduction of the mass of the pancreas and in the present paper have been discussed the changes in metabolism resulting from the reduction of body mass in the form of reserves, especially fat, by alteration in diet. It now remains to discuss the changes resulting when the body mass is suddenly reduced through loss of body tissue, such as may occur following extensive

⁸ Allen, F. M.: AM. JOUR. MED. SC., 1917, p. 153, Chart VIII.

injury, or following amputation. The latter is unfortunately frequently necessary in diabetic patients. Diabetic gangrene is still only too prevalent and if the infection is extensive thigh amputations are the rule. Occasionally both legs are thus lost. More often, with advanced arteriosclerosis and doubtful prognosis, the question must be decided whether to amputate at once or spend months in a risky attempt to save the limb. If a marked gain of assimilative power could be expected from the removal of one or both legs there are cases in which this would determine the choice. On the other hand, if there is danger of any lowering of assimilation from the removal of large masses of muscle this also should be known.

Theoretically it would seem possible that there is a quantitative relationship between the pancreas and the mass of body tissue which it must supply with hormone. As previously remarked, it must be impossible for the pancreas of a mouse to supply the body of an elephant. It is conceivable that the effects of over- and undernutrition may be due to changes in the mass as well as the activity of living protoplasm, according to one well-known theory. This involves also the question whether the pancreatic function pertains to the endogenous or the exogenous metabolism in the sense of Folin. Determinations of the urinary creatinin and uric acid in human patients would have been simple and instructive, but were prevented by circumstances; and those actually begun in dogs failed by reason of the difficulties already mentioned (in that the dogs chosen for the purpose prove unsuitable or meet with accidents), and repetition was not possible. It is evident, however, that sudden loss of a considerable bulk of cells carries away everything pertaining to these cells in both mass and metabolism, and the effects can be compared with those of a similar reduction of weight resulting from diet. There is some possibility that the effect may be much greater. Another possibility is that the loss of important masses of sugar-burning tissue, especially muscles, may lower the total capacity for sugar utilization.

Opportunities have occurred for the observation of dogs (both normal ones and those rendered diabetic by removal of portions of the pancreas), that have lost large amounts of body tissue suddenly. In one instance the loss was over 20 per cent. of the body weight. Tests made on these dogs by means of intravenous injection of sugar showed no definitely increased tolerance for carbohydrates in any of them.

The opinion that the endocrine pancreatic function is concerned in exogenous rather than endogenous metabolism is in line with certain theoretical deductions. If it has been possible to perform the desired analyses in clinical cases there is reason to anticipate that obese patients whose body protein is protected by diet and who are merely reduced in fat will not show any reduced output

of endogenous creatinin and uric acid. Yet diabetics of this type gain greatly in assimilative power under this program. Such a research would establish that the internal pancreatic function is not connected with the endogenous metabolism, so far as the latter is chemically measurable.

A practical point not covered by the animal observations is the assimilation per kilogram of the reduced body mass and the lower food requirement of a patient who has lost one or both legs. An indirect benefit to the diabetes from this fact can scarcely be doubted, but the point has no theoretical significance in the present connection, and as a practical measure it is scarcely to be mentioned in comparison with the therapeutic method of reducing the metabolism by undernutrition.

Conclusions. 1. The assimilative power of diabetic animals rises and falls inversely with the body weight. This change is established on different diets, which exclude the supposition that it is due merely to variations in either glycogen or protein, and which prove that it is produced also by the feeding and deposit of a non-sugar-forming material, namely fat.

2. When considerable masses of active tissue, especially muscle, are removed by amputation, the effects upon the assimilation are negligible compared with those of similar losses of weight produced by undernutrition. It may therefore be concluded that the effects of undernutrition are not due to a reduction of active protoplasm but rather to a reduction of food supplies and metabolism. Though there must necessarily be some relation between the mass of pancreas and the mass of body cells which it can supply with hormone, this research indicates a direct quantitative participation of this hormone in the metabolism of matter, and furthermore in exogenous rather than endogenous metabolism. In other words, the pancreatic function is not appreciably spared when the same quantity of food is metabolized by a reduced number of cells, but rather when the same number of cells metabolize a reduced quantity of food materials.

3. This principle is important clinically in that undernutrition should be continued to the point of relieving the pancreatic function from overstrain revealed by the most delicate tests, particularly hyperglycemia. With extremely few exceptions in human patients the curve of rising tolerance intersects the curve of falling weight at some level on which life can be maintained. Lack of thoroughness in relieving the pancreatic function is the chief cause of continued deterioration of this function and the consequent choice between coma and starvation. The present investigation has aimed at something more than an empiric treatment, namely, the valid proof of a quantitative relation between the internal pancreatic function and the total body weight and metabolism. Any theories of the nature of this function or of diabetes must

take account of the fact that the islands of Langerhans are concerned not merely in the combustion of sugar or storage of glycogen, but also in the maintenance of the general tissues and reserves. In some manner an increased supply of fat or formation of adipose tissue imposes a burden on the island function, and reduction of any kind of food or of the body weight reduces the demand upon this function. This fact seems to indicate that the island hormone has both a catabolic and an anabolic role.¹⁰

As the diabetic deficiency is so much more prominent with regard to carbohydrate, it is possible that the function is directly related to this alone, and that other foods are concerned only indirectly through their influence upon carbohydrate metabolism, though this point remains unproved. Whether the relation be direct or indirect, the status of the pancreatic hormone in general metabolism and of the disturbance of general metabolism in diabetes is sufficiently important that treatment must be directed to it and is seldom successful if limited to restriction of carbohydrate alone.

BENZYL BENZOATE IN PEDIATRIC PRACTICE.

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THE writer became interested in this subject several years ago when Dr. David I. Macht was first working with this interesting and useful preparation.

Macht showed that the action of the opium alkaloids on smooth muscle fiber bears a direct relation to the chemical structure of the drug. The morphin group tend to stimulate contraction and to increase the tonus of smooth muscle while the papaverin group tend to inhibit contraction and to relax the tonus. He showed, further, that the stimulating action, on the one hand, is due to the pyridin part of the molecules and the relaxing properties to the presence of the benzylic grouping in their molecules. A search was made for a substance with a benzyl radical which would have the same action on smooth muscle but be free from toxic and narcotic principles. Macht finally settled on benzyl benzoate, a well-known organic ester, in commercial use in the manufacture of perfumes.

Benzyl benzoate, Macht also determined, was largely excreted in the urine as hippuric acid.

On the smooth muscle, benzyl benzoate inhibits the rhythmic contractions, lowers the muscle tone and relaxes spasm. The action

¹⁰ Taylor, A. E.: Tr. Coll. Phys., Philadelphia, 1916, xxxviii, 254. Cf. Rockefeller Institute Monograph, 1919, No. 11, p. 128.

on the intestinal movements is similar to atropin, an inhibition of peristaltic action. On the uterus, gall-bladder and the urinary bladder the action is antispasmodic, inhibiting the contractions and causing relaxation. On the circulation the action is chiefly on the peripheral vessels, a fall in pressure due to the relaxing of the arterial muscles. As ordinarily administered the effect on the circulation may be disregarded, although it is given by mouth for its action on arterial hypertension. Ordinary doses do not affect the heart or respiration except as they may produce a quieting effect on the respiratory centers in certain pathologic states. Such doses do not affect the central nervous system and only very large doses affect the general musculature.

Therapeutically, Macht found the uses of the drug to be very much those which would be anticipated, *i. e.*, the inhibition of peristalsis and the relaxation of the spasm of smooth muscle.

In infants and young children many distressing symptoms are caused by the great tendency to spasm of the smooth muscles, and a brief consideration of the uses of benzyl benzoate in pediatric practice may be of service in stimulating further study of this drug, which, it would seem, bids fair to become a permanent part of our armamentarium.

On general convulsive conditions its action is often most favorable. This, perhaps, would scarcely be expected, but the clinical results have been very striking in infants who were having repeated convulsive seizures. There are certain children, and there are certain conditions, which doubtless cause a similar condition in any child, in which general convulsions are brought on by reflex action from what appears to be very slight causes, the so-called spasmophilic diathesis in the instance first named. One or two illustrative cases will suffice.

1. An infant, four days old when first seen. Delivery had been normal but a circumcision had been performed immediately after birth. This wound had become infected, and what appeared to be a general septic condition resulted. At some time each day the temperature reached 104° or 105° F. Omitting other irrelevant details it may be stated that the child was having forty to fifty convulsive seizures a day. The slightest movement about it was sufficient to provoke an attack. During the physical examination the child was in a constant state of spasm. Lumbar puncture was tried but no fluid could be obtained. Four-drop doses of benzyl benzoate, sufficiently diluted, were given and later the dose was diminished to one or two drops at four-hour intervals. The effect was all that could be desired. The number of convulsive seizures was diminished to about half dozen a day, the child was able to nurse with comfort and it eventually made an uneventful recovery.

2. A child of three, of extremely nervous parents and very nervous

itself, with the history of frequent convulsions, ate a variety of indigestible articles of food and started in with convulsions at frequent intervals. The stomach and bowels were emptied, but the convulsions persisted. Benzyl benzoate was administered in ten-drop doses and a condition of quietude resulted.

The first trials by the author were in whooping-cough. This disease presents certain peculiarities, among which is the notoriously uncertain action of antispasmodic drugs. What quiets one child will have but little effect in another. Taken all in all, belladonna or atropin gives the best results in the greatest number of cases, but atropin is a drug which cannot be left indiscriminately in the hands of the ever-increasing careless, and the same is true of most of the other powerful antispasmodic drugs. Benzyl benzoate acts fairly well in many cases, lessening the number of attacks of coughing and so making the patient more comfortable. The action is, however, uncertain. In some instances the relief is striking while in others it is practically *nil*. This may be due to lack of knowledge in the dosage, and it may be that in the resistant cases larger amounts would produce the desired effect.

In cases of bronchial asthma and in spasmodic bronchitis the effect is most happy, and in the author's experience most certain of all the diseases in which he has used the drug. The wheezing case of bronchitis is almost always converted into one with easy, silent respiration while the asthmatic is rendered tolerably comfortable, and this without the undesirable concomitant effects of most of the drugs ordinarily employed.

In colic due to spasm of the gastric or intestinal muscles relief is usually prompt, and in hiccough, sometimes a very uncomfortable symptom in early life, the results are more satisfactory than with any other drug with which the author is acquainted. Of course, the transient hiccough so commonly seen in young infants rarely needs treatment. In only the more severe and prolonged attacks is anything needed.

Of more importance and worthy of thorough investigation is the use of benzyl benzoate in pylorospasm. Of course, one should differentiate the cases in which the spasm predominates from those in which the obstruction is chiefly due to hypertrophy. Many cases supposed to be the latter may be permanently relieved by the use of antispasmodics, and the author has a long list of such cases in which atropin or papaverin has been successfully used. In fact, atropin has proved so satisfactory that the trial of any substitute made but little appeal. There are, however, cases in which the amounts of atropin required to cause relaxation will produce slight toxic symptoms, such as dryness of the mouth and throat and dilatation of the pupils. In such cases benzyl benzoate is of service and it has been successfully used in others. While apparently non-

toxic the taste and burning sensation make it more difficult of administration. For those unfamiliar with the correct dosage of atropin it is perhaps safer; but the fact remains that atropin poisoning rarely, if ever, kills and is not liable to occur except when simple directions cannot be followed.

In diarrhea in which there is excessive peristalsis, benzyl benzoate may be used to check the excessive movements, and it does not check secretion and it may eventually replace opium in cases in which there is a doubt as to the propriety of using opium.

In spastic constipation it is also of value. Curious cases of this are not infrequently met with in children, and may even find their way to the operating table. Atropin has been the chief reliance, but benzyl benzoate is of positive value. One instance may be cited:

3. A previously healthy fifteen months' old boy was taken suddenly in the early morning with severe pains in the abdomen, vomiting and a certain amount of prostration. Castor oil was immediately administered by the mother and an enema given resulted in a small stool. The castor oil was without effect. Following the enema there were no more bowel movements and a repetition later in the day brought away only a little mucus. The vomiting continued. He was first seen about thirty-six hours after the onset and after various drugs had been given without relief and the question of operation for obstruction had arisen. Ten drops of benzyl benzoate properly diluted were retained and in about an hour there was a copious evacuation, with immediate relief of pain and vomiting.

Several similar cases have been seen by the author in which atropin hypodermically in full doses gave relief; in one, a child of two, who was supposed to have an obstruction of the intestine. The child had eaten heartily of some dry, branny breakfast food. Some time later in the day there was vomiting and a bowel movement, great pain referred to the abdomen and prostration. Repeated enemas and purgatives gave no relief. When seen, thirty hours later, the child was greatly prostrated and a mass could be felt in the lower part of the epigastric region, somewhat to the right. A rectal examination brought away a small amount of fecal matter mixed with some particles of the food. A large dose of atropin gave relief and a large quantity of breakfast food was passed. It had evidently passed rapidly through the stomach and swelling in the intestine through the absorption of fluid and caused a spasm of the intestinal muscles above and below. The antispasmodic action of the atropin relaxed this, just as benzyl benzoate had caused relaxation in the case reported.

It hardly seems necessary to quote case histories illustrative of each phase of the usefulness of this drug. It would seem that in a

remarkably short time its place has been definitely made and one can safely predict it will continue in use until replaced by something better, or, at least, newer. Its limitations are scarcely known as yet but may easily be surmised. The dosage offers the greatest difficulty.

The author's experience has been limited to the use of a stable preparation prepared by Mr. H. A. B. Dunning, of Hynson, Westcott & Dunning, of Baltimore. Adults may take a dram of this at intervals of four to six hours as in dysmenorrhea. Macht gives the adult dose as 20 minims, but this will be found to be too small in many instances. For children the dose may be scaled down. Assuming the adult dose to be suited to 150 pounds, use either the amount obtained by the fraction of the child's weight and 150 or use Young's rule of the age divided by the age plus 12. Apply either of these to 60 minims as the maximum dose (not necessarily) to 40 minims as an average dose and 20 minims as a minimum dose.

The drug is hot and unpleasant to most children and must be diluted with water, sweetened water or milk. Older children may take it dissolved in olive oil and put up in capsules, but plenty of water should be taken at the same time. Carminatives are recommended to make the dose more palatable, but their use is of questionable value. Ampoules of benzyl benzoate in olive oil may also be had for hypodermic use when very rapid action is desired. When given by this method the drug should be injected intramuscularly.

The drug seems non-toxic. The author observed an instance when a dram was given by mistake to a child of six years. Apart from a disagreeable burning sensation in the mouth, throat and epigastrium no ill effects were noted. Whether the effects of the drug wear off with continued use, *i. e.*, a tolerance established, has not been determined.

Conclusions. Benzyl benzoate is a valuable addition to the armamentarium of the pediatricist. It may be used in place of atropin wherever a relaxing effect is desired on spasm of smooth muscle.

The author has used it sufficiently to be able to recommend it in bronchial asthma, spasmodic bronchitis, gastric or intestinal colic, hiccough and spasmodic constipation.

It has been recommended by others in excessive peristalsis.

In whooping-cough its action is often most beneficial, but the results are uncertain, as is the case with all other antispasmodics in this disease.

In general convulsive conditions not dependent on organic lesions of the central nervous system, especially in the newborn, the drug will be found of benefit.

It is non-toxic but not particularly agreeable to take.

STUDIES IN THE PHYSIOLOGY OF THE LIVER: I. TECHNIC AND GENERAL EFFECTS OF REMOVAL.

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THE relatively large size of the liver, its double blood supply, and its elaboration of an internal and an external secretion have contributed to make the organ a source of continual interest to the physiologist. Many problems concerning its function are not definitely understood or are still under debate. They have been investigated by the removal of the liver and a study of the effect on the organism. The usual method has been to modify the function of the organ by performing an Eck fistula and ligating the hepatic artery, leaving the organ in place, the animal being kept under an anesthetic throughout the period of observation. This method may be satisfactory for the investigation of some problems, but the autolysis and absorption of the remaining liver tissue is a serious complicating factor. For instance, cutting off the blood supply to one lobe of the liver of a dog by ligation usually makes the animal very sick within a short time and causes its death in less than twenty-four hours. Various lobes of the liver have been removed by repeated operations, but the remaining portion always regenerated so that a permanent deficiency of liver tissue was not produced. In one of my experiments the surgical removal of approximately 70 per cent. of the liver was followed by practically complete regeneration in the course of a few months. The same condition follows the functional removal of the liver tissue by ligating the ducts. I have been able to ligate the ducts that drain approximately 70 per cent. of the liver without producing any effect on the animal's general condition. The ligated portion of the organ has undergone biliary cirrhosis and the unligated portion regenerated to make up for the loss of functioning liver tissue. The complete removal of the organ has been complicated by its relation to the portal circulation and the vena cava.

The portal circulation can be taken care of easily by an Eck fistula, but the intimate relation of the liver to the vena cava in most species of animals is such that complete removal of the organ rarely can be accomplished without damage to the venous return from the extremities. If damage to the vena cava is avoided, liver tissue is always left. Usually the remaining tissue is without blood supply and undergoes autolysis, producing a definite toxic effect.

For the study of some problems in the laboratory it seemed desirable to know definitely the course of events following the removal of the liver under conditions complicated by no factors other than the

anesthetic used at operation. None of the methods previously described fitted our purpose. Accordingly the method herewith reported for the removal of the liver of the dog was developed. The success of the method depends on the fact that the portal capillaries offer more resistance than collateral venous channels and as a result collateral circulation develops through other venous channels.

Technic of Removal of the Liver. The operation is performed in three stages. Ether anesthesia and sterile technic are employed. In the first operation an anastomosis is made between the portal vein and vena cava in the manner followed in performing an Eck

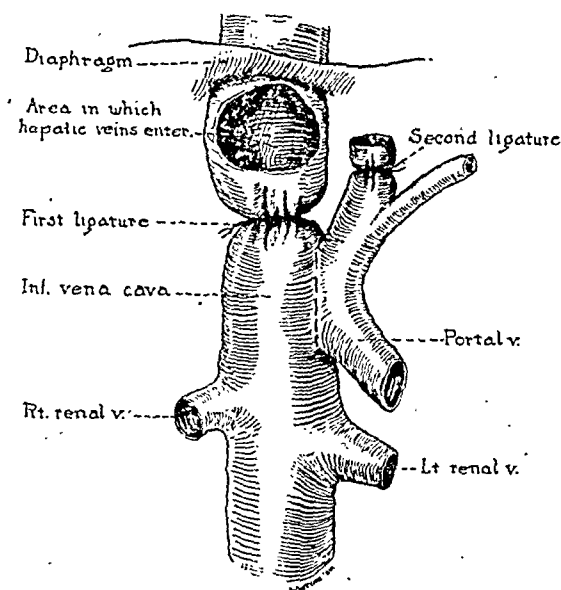


Diagram illustrating the steps in the technic of the removal of the liver. At the first operation the portal vein and vena cava are anastomosed along the dotted line and the first ligature is placed. At the second operation after the collateral circulation has been established the second ligature is placed. At the third operation the liver and the portion of the vena cava between the ligature and diaphragm are removed.

fistula, except that the vena cava is ligated instead of the portal vein. The ligature is applied just proximal to the entrance of the right lumbo-adrenal vein. This produces an increased pressure in both the vena cava below the ligature and in the portal system. Since the liver capillaries offer more resistance than that necessary to develop a collateral circulation through the azygos and internal mammary veins, in a short time most of the blood from the extremities will be passing through the latter route. The collateral circulation develops to such an extent that in three or four weeks after the first operation the second can be performed. The portal vein is ligated at the usual site in performing an Eck fistula, after which

all the blood from the posterior extremities and the portal system passes to the heart through the peripheral collateral circulation, see illustration. At the third operation the liver is removed completely by ligating the hepatic artery, the vena cava just below the diaphragm, and whatever small collateral veins have developed along the gastrohepatic omentum.

As in all experiments in which more than one operation is necessary, every experiment was not successful. In animals in which the diameter of the portal vein is narrow it is not always possible to ligate the cava without producing too much pressure in the portal system. Sometimes thrombosis occurs. In some animals the collateral circulation does not develop sufficiently to permit ligation of the portal vein. In a few cases a collateral circulation through thin-walled veins developed around the field of operation and resulted in unavoidable hemorrhage at the final operation.

The development of the collateral circulation has been interesting. In some animals, especially females, the superficial abdominal veins have returned most of the blood, anastomosing through the internal mammary veins. A very marked caput medusæ developed in these cases. In other animals there was little dilatation of the peripheral veins, the collateral circulation developing through the deep vessels. In some animals a considerable collateral circulation developed through the capsular veins of the kidney. In one animal the vena cava thrombosed throughout its entire length from the ligature to below its bifurcation. The animal lived for several weeks with the blood from the kidneys returning through the capsular veins. In some animals the esophageal anastomosis was markedly developed.

The length of time between the different operations varied. In most instances it was at least a month and longer between the second and third operations.

Most of the animals remained in good condition throughout the entire period of observation and afforded us an opportunity to obtain some data with regard to the Eck fistula and the reverse Eck fistula. Few facts of value can be obtained concerning the reverse Eck fistula unless the collateral venous return has been occluded. Since the blood flow through the liver was but temporarily increased this probably explains why little of note had previously been observed in a study of the latter.

Every effort was made to perform the final operation as quickly as possible and to use a minimum of the anesthetic. The removal of the liver from the beginning of the anesthetic seldom required more than one hour, and the animal recovered almost completely from the anesthetic within another hour. Artificial heat was usually supplied until the animal fully recovered. This was not found to be essential, however. The widely dilated veins usually occasioned some hemorrhage, but only infrequently sufficient to constitute a

serious complication. Such data as a pulse-rate, respiration, and temperature were taken before and at various intervals after operation.

An excellent illustration of the mechanical function of the liver in offering resistance to the diaphragm was obtained in the first experiment in which the third stage was attempted. After the liver was removed the animal's respiration remained very shallow. Artificial respiration by manual means was instituted to assist recovery. To our surprise the animal died immediately after the artificial respiration was started. Necropsy showed that the thoracic compression had ballooned out the diaphragm at the former site of the liver, and, owing to the lack of resistance previously offered by the liver, a simple exchange of pressure between the thoracic and abdominal cavities resulted without any exchange of air in the lungs. In the subsequent operations insufflation was employed and no further trouble was encountered.

Results of Removal of the Liver. In general the course of events following removal of the liver has been quite constant in the different animals. It was anticipated that by carefully following the technic described it would be possible to keep a dog alive for a considerable length of time. This hope was not realized as all the animals in this series died within five to eleven hours after operation. But even though the length of life after operation was short we were able to observe the course of events subsequent to total loss of liver function and under conditions closely approximating normal.

The period of recovery of an animal from the anesthetic and from the immediate effects of the removal of the liver does not seem to differ from the period of recovery following other operations; in our series it varied from one hour to two hours. After the animal recovers from the anesthetic there is an interval which in this series of experiments varied from two to eight hours, during which the animal appears to be normal. It then becomes moribund and usually dies quickly, within one or two hours.

Before the animal develops the symptoms apparently of loss of liver function, its condition as to pulse, respiration or temperature is identical with that of an animal at a corresponding time following any other operation which has involved a similar period of time, amount of trauma, and anesthesia. During the period following the recovery from anesthesia the animal walks around, responds to call, drinks water and sometimes milk. To all appearances it is normal, except, of course, for the signs of a recent operation.

The onset of the moribund period is usually sudden and the first sign is muscular weakness. The animal prefers to lie down, and when standing it cannot hold itself erect or avoid swaying when walking. Usually within an hour after the first evidence of muscular weakness the animal is unable to rise, but lies quietly breathing, with muscles flaccid and relaxed.

The period during which the animal is quiet is usually short. It is soon noted that a loud noise or a jarring of the table upon which it lies produces a stiffening of the limbs. Muscular twitchings develop and later definite convulsions occur. The twitchings may involve only one muscle in a limb or a whole group of muscles. They are both tonic and clonic in character. Usually shortly after the muscular twitching has developed a very slight noise or a sharp slap produces a general convulsion. Some of the muscular spasms last one-half minute or more.

Often the animal exhibits movements similar to those employed when trotting; just before death it attempts to vomit and the slightest stimulation around the region of the head produces a snapping of the jaws as though at an imaginary foe. Death follows a convulsion, involving seemingly all the muscles of the body.

After the removal of the liver the pulse is more rapid than normal, but not more so than is usual, following other comparable operative procedures. After muscular weakness develops the pulse decreases but does not go below normal.

The respiration always becomes rapid and frequently of the Cheyne-Stokes type as the animal develops the moribund condition. Death is respiratory rather than cardiac; respiration in our animals has always stopped before the heart.

Contrary to expectations the temperature continues normal until the animal becomes comatose, when it may become subnormal. An interesting observation is that in some of the animals the temperature may go a degree above what it was previous to operation just before muscular weakness develops.

No findings at necropsy have as yet been noted which could be attributed to the loss of the liver.

In many respects the syndrome following the loss of liver function is typical of the syndrome following the total removal of the adrenal glands; the initial development of a muscular weakness is quite similar. On the other hand the muscular twitchings, and, particularly, the muscular spasms and the character of the respiration recall parathyroid tetany. The condition following removal of the liver, however, is, on the whole, a definite entity.

Since the preparation of an animal for the final operation of removal of the liver takes considerable time and there are some failures at the various stages, so far only a small series has been studied. This series, however, has shown conclusively that a definite and constant series of events occurs after complete removal of the liver tissue and a collection of data has been begun with regard to the changes which take place in the organism during the period the animal appears normal.

The data so far obtained do not justify many positive statements of the events after the removal of the liver or the cause of death.

There seems to be some change in metabolism whereby some intermediate toxic product is produced or some necessary element for metabolism is lacking. The process is probably of the same general nature, although of somewhat different characteristics than that following the removal of the adrenals or the parathyroids.

Special observations were recorded in a few cases:

1. One animal was transfused with blood and saline solution shortly after the first symptoms were noted. The usual course of the reaction did not seem to be affected by this procedure.

2. One animal was fed on a diet of liver for two weeks before the final operation. Except that the convulsions were more marked the results did not differ from those in other animals.

3. In two animals the carbon dioxide combining power of the plasma was estimated just before operation and again after the onset of the moribund condition. In both instances it was initially rather high and decreased slightly after operation, but not enough to account for any of the symptoms.

4. In one animal blood creatinin and in two animals urea determinations made before operation and during coma yielded normal values.

5. While careful estimates of the clotting time of the blood have not been made, gross observations have not revealed any difference. In one experiment blood removed just before death clotted in six minutes.

6. In two experiments in which observations were made bile appeared in the urine and in the plasma after operation; it was not present before operation.

7. In three animals the urine was tested for sugar after operation; sugar was found in one, but it disappeared before death.

8. In one experiment the blood sugar was estimated at various periods after operation. It progressively decreased to less than half its normal value.

Summary. A method is described for the total removal of the liver of a dog without complicating factors other than the anesthetic. This makes it possible to study the effect resulting solely from the loss of liver tissue. An animal from which the liver is removed by this technic recovers from the immediate effects of the operation and then presents a definite and characteristic syndrome, a sequence of events invariably ending in death. The length of life after removal of the liver in this series of experiments has been from five to eleven hours.

**ALIMENTARY HYPERSECRETION; GASTRIC HYPERSECRETION;
GASTROCHRONORRHEA.**

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WE are in the midst of a period in clinical gastric research wherein the attention of the majority of workers is focussed on diseases characterized by organic or structural changes in the tissue wall of the stomach or duodenum. Ulcer and cancer are the all-absorbing topics of discussion, and not without good reason. The advent of the roentgen ray, with its marvellous ability to portray defects and distortions of the borders of the organ, has given a strong impulse to the study of structural diseases. In so doing the observations of functional disturbances have fallen into the background and a lesser interest and eagerness have been shown in attempting to reclassify and evaluate the various forms of secretory disturbances to which the stomach, as a major secreting organ, is subject.

The total daily gastric secretion is no inconsiderable factor in the human physiology. It is estimated in amount as normally up to 1000 c.c., being thus second only to that of the kidney, though in composition its excretion is much more simple and chemically less complex. The older methods for the study of this secretion lay entirely in the use of the single test-meal, be it Ewald, Riegel, Sahli or other. Such a method was inadequate and unsatisfactory and contributed much to the lack of interest in the functional gastric diseases.

The introduction of a newer and improved method for withdrawing specimens of stomach secretion, the fractional test-meal, has given us an opportunity to look back over some of the older though still mooted questions in gastro-enterology in the hope that the application of such a method would throw a new and elucidating light on disputed points still far from settlement.

The topic of hypersecretion is just such a one. It has remained to date still a point in debate as to whether gastric hypersecretion was a normal phenomenon or whether it was a purely nervous phenomenon or whether after all hypersecretion was a manifestation of ulcer. Boas,¹ as recently as 1911, says that the significance of this phenomenon remains with future students to interpret, and though frequently expressing his personal

opinion in a discussion of the facts, always guards himself against some future reversal of his stand on any point.

— Since Reichmann,² a practising physician in Warsaw in 1882, first described a case which he called "Magensaftfluss," up to quite recently, a prodigious amount of energy and effort has been spent in attempting to elucidate the clinical and chemical picture which he presented. Reichmann described a single case characterized by the presence in the fasting stomach of a large amount (100 to 1000 c.c.) of a fluid, bearing all the properties of pure gastric secretion. Clinically the patient suffered from progressive emaciation, headaches, vomiting, pyrosis, eructations and postprandial pains, particularly severe at night. Reichmann regarded his case as a functional secretory overactivity of the gastric glands; six hours after a full meal he was able to remove by lavage two and a half liters of gastric contents, containing food, sarcinae, yeast and much hydrochloric acid. He does not suggest the possibility of ulcer nor does he mention ulcer as a possible factor underlying the complaint.

His publication aroused much discussion and brought out many publications, among the most important of which were those of Jaworski and Glucinski,³ Riegel,⁴ Schreiber,⁵ Rössbach,⁶ Jurgensen⁷ and others. The discussion hinged mainly on the point whether Reichmann had described a rare and very unusual condition or whether hypersecretion was not, at least in its milder grades, a rather common clinical phenomenon. The dispute centered mainly upon the amount of fasting contents that could be called normal. Rosin,⁸ Riegel,⁹ Martius¹⁰ and Strauss¹¹ found in the normal fasting contents not over 12 to 20 c.c. of fluid. Boas,¹² Huber¹³ and particularly Schreiber⁵ found normally up to 50 and 100 c.c. These authors, being unable to agree upon an accepted maximum figure for the amount of fasting contents, were unable to agree as to what to call hypersecretion and what to call normal. Riegel,⁹ who believed that the normal fasting stomach should be nearly empty, found many cases which he regarded as mild hypersecretion, while Schreiber,⁵ whose normal standard was much higher, regarded real hypersecretion as excessively rare. Jaworski¹⁴ found the condition present in 115 of 159 cases examined. In 1887 Reichmann¹⁵ contributed a more complete study of the syndrome he had originated. He described many cases in which the phenomenon occurred periodically, attributing the findings to various conditions of nervous irritability such as tabetic crises, hysteric crises, etc., but was able to collect in these five years only six real cases wherein pure continuous hypersecretion occurred, independently, in his opinion; of any organic lesion.

From this time to the present the discussion continues as to the occurrence of the disease as a clinical entity and as to the interpretation of continuous hypersecretion when it does occur. In general it may be said that differ as they might on the incidence of the

disease, nearly all agreed that hypersecretion was a symptom of functional overstimulation of the gastric glands through excessive nervous excitation.

The advent of the period of gastric surgery introduced an entirely new and very valuable factor. The increasing recognition of gastric and duodenal ulcer as an etiologic factor in abdominal disorders caused a reclassification of diseases of the stomach. One notes, particularly in this field, the swing of the pendulum in favor of organic explanations, Soupault¹⁶ operated upon 58 cases of so-called gastrosuccorhea and reported finding ulcer in all. Hayem¹⁷ and Mathieu,¹⁸ leaders of the French school of gastro-enterologists, accepted this view with few reservations. Boas¹ in the 1907 edition of his book was undecided, but in the 1911 edition he attributes at least two-thirds of the cases to gastric or duodenal ulcer though admitting the existence of some of the cases upon a purely neurotic basis. Ewald,¹⁹ however, still clung to his opinion of a real neurosis as the basis of the phenomenon.

Interest in the subject of the milder forms of hypersecretion as one phase of the gastric physiology of digestion was actively renewed when Strauss,¹¹ in 1903, pointed out the very common occurrence of hypersecretion in numerous gastric disorders. Strauss, and those that took sides in the discussion which he aroused (Zweig, Calvo, Huppert, Grandauer), laid little emphasis on the amount of fasting contents. They described "alimentary" hypersecretion, that is, an excessive digestive secretion occurring during and after the period of active digestion. To them "Reichmann's disease," or continuous hypersecretion, was a rare and much exaggerated form of alimentary hypersecretion. In its milder form it occurred in 31 per cent. of all male cases, and 8 per cent. of all the female cases examined. These authors were divided as to its interpretation; the weight of opinion, however, favored hypersecretion as being a state of increased secretory stimulation, in the largest percentage due to ulcer or other intrinsic gastric causes.

This rather prolonged review of the literature should be pardoned by the reader. There is so much of confusion associated with the phrase "gastric hypersecretion" that it has been deemed not superfluous to collect the opinions of those who have previously been interested in this topic. Summarizing these efforts, one distinguishes the following:

A. *Continuous Hypersecretion* (Magensaftfluss or Reichmann's disease), a malady having a characteristic clinical picture and evidenced by continuous outflow of large quantities of secretion both in the digestive and interdigestive and fasting states. Surgery has pretty nearly classified most of these as cases of pyloric stenosis due to ulcer; the medical men succeeded in establishing a smaller number on the basis of pure neurosis.

B. *Continuous Hypersecretion*, occurring not chronically but in intermittent form, associated with periodic migraine, tabetic crises,

paroxysmal hysterical vomiting spells, etc. These are accepted by all as cases due to excessive stimulation of the gastric nerves of central nervous system origin.

C. *Alimentary Hypersecretion*, not really a disease but a symptom or chemical phenomenon occurring during digestion. This milder form of secretory stimulation was shown to be a very common phenomenon and generally attributed to protopathic organic origin, usually ulcer.

The fractional test-meal as a means of studying gastric physiology and chemistry, having introduced a new and undoubtedly valuable clinical method, it has been deemed warrantable to reopen this subject for investigation. The Ewald test-meal furnished information of the activity of the stomach at its supposed height or one hour after the ingestion of a simple meal, but it can readily be shown that hypersecretion when it does occur, takes place almost entirely after the fastigium is reached or in the declining stage of motor activity. The very definition of *magensaftfluss* or *gastrochronorrhoea* (Hayem) is secretion activity after the digestive cycle and in the interdigestive cycle. Hence the fractional method has furnished an ideal means for studying the digestive, postdigestive and interdigestive states. In so doing it has established an entirely new criterion upon which to base the judgment of what is or what is not a normal amount of gastric secretion, and what is the clinical significance of an outflow of digestive juices when it occurs to an abnormal degree. In fact, Hayem²⁰ who years ago used repeated test-meals, extracting them on successive days, one-half, one, one and a half, and two hours after ingestion, introduced the term *gastrochronorrhoea* as an improvement on the term *gastrosuccorrhoea* to indicate an abnormal secretion in the post and interdigestive periods. When discussing this disease his attention was entirely focussed on this phase of the subject.

In the fractional test-meal as at present employed, with the indwelling tube of Rehffuss, and using oatmeal gruel as a test substance, it is simple to determine the amount of secretion poured out by the secretory acini in proportion to the residue of gruel in the stomach at any given period.

The fasting stomach contents being first removed and the gruel meal being drunk, successive fifteen-minute specimens are withdrawn until no further material can be aspirated. The first quarter of an hour specimen is normally nearly all gruel, or at least four-fifths gruel and one-fifth secretion. At the end of the half-hour there is still at least two-thirds gruel and one-third secretion present. By the end of the first hour the stomach has produced about as much secretion as there is gruel in the viscus, always remembering, of course, the fact that gruel is constantly passing out of the stomach through the pylorus. In the successive periods the secretion becomes relatively more abundant and the gruel less in amount, until by the sixth or seventh quarter-hourly specimen there is only one-sixth to

one-eighth of gruel present in the test-tube, upon settling, all the remainder being secretion produced by the glands. At the end of one and three-quarters to two hours the stomach has expelled the last trace of gruel (iodin-starch test negative). Normally the glandular secretion ceases after this period and further attempts to aspirate either meet with no success or bring up only two or three c.c. of mixed gastric mucus and saliva. The stomach as a secretory digesting organ has come to rest. If the secretion of the stomach, now more properly called parasecretion (Boas), continues we have the phenomenon of hypersecretion or supersecretion. This hypersecretion may be present during the latter stage of the normal digestion, as evidenced by the greater proportion of secretion to gruel in the withdrawn specimens; and it may and usually does last for one-half to one hour after the organ has completely evacuated the food. This we recognize as alimentary hypersecretion. If the parasecretion is present during the second, third and fourth and later hours of the postdigestive cycle we recognize a continuous hypersecretion, or gastrochronorrhea.*

The following original studies have been made upon 50 cases in which sixty-eight fractional tests have been made. The cases were collected in the medical wards of Mount Sinai Hospital, a smaller percentage being added, from the private practice of the writers. Clinical observations were maintained for a period in each case of several weeks; in many of the cases the observations extend over months and in some years. Careful clinical and chemical studies, exact roentgenologic observations, and in many cases findings at the operating table tend to form as complete a collection of data as is possible, upon which to base a diagnosis of the underlying condition. Cases in which a definite and marked delay in motility was present have been excluded particularly if food residue or sarcinæ and lactic acid were present in the fasting contents, as these cases were evidently examples of pyloric stenosis of organic origin and not simple hypersecretion. In these cases there being practically no interdigestive state but just one continuous stage of digestive activity, we are unable to judge of the condition of the organ in the usual resting period.

Incidence. - It is impossible to judge of the frequency of the occurrence of hypersecretion in the hospital, as no statistics have been kept of the total number of fractional test-meals taken. At Mount Sinai Hospital the fractional test is employed almost as a routine test; the number of observations is therefore very large. An idea of the incidence of hypersecretion is more easily judged from the cases seen in private practice. Of the last 100 fractional tests taken in the office by the authors twenty showed definite hypersecretion (20 per cent.). This figure is lower than that of Jaworski,¹⁴ who found 115 instances in an examination of

* Strauss,¹¹ using a test-meal of dry crackers, recognizes a percentage of dry residue to secretion greater than 1 to 4 or 5 as a case of hypersecretion.

159 patients. (As was previously noted, Jaworski judged almost entirely on fasting content findings.)

As a symptom, hypersecretion is anything but rare. When Reichmann² first described the syndrome it was regarded as unusually uncommon. The later writers, as well as these figures, prove it to occur in at least 1 out of every 3 cases examined.

Sex. The male sex predominates greatly, 88 per cent. of the cases being in males. This agrees with the data of the older investigators.

Age Incidence. There are no observations below the ages of twenty and none over seventy years. Approximately 55 per cent. of the cases occurred between thirty and fifty years of age, 16 per cent. between twenty and thirty years.

Seasonal variations are not noticeable.

Laboratory Data. In cases of hypersecretion the fasting contents of the stomach is increased. It is useless to enter into a discussion as to the maximum amount of secretion found in this viscus in the morning before the first meal has been taken (*liquid à jeun*). Estimates of various authors show a wide range, most of them lying between 10 and 20 or 30 c.c. However, many other writers include any amount up to 50 to 100 c.c. as normal. These latter figures are too high in our experience. The fasting content in many hundreds of cases is normally rarely more than 30 c.c.; larger amounts indicate abnormal secretory activity or delayed motility, or both. In this series of 50 cases of hypersecretion the resting stomach in the morning contained on an average 65 c.c. The actual figures lie between 0, found only once in a case of achylia with hypersecretion, and 180 c.c. in a case of ulcer with normal range of acidity but marked hypersecretion. Findings of 90, 120, 130 c.c. or more are common. The fluid withdrawn is always clear, watery, slightly milky or cloudy and shows a faint admixture of bile and salivary secretion. Food residue is never present in cases of pure hypersecretion without organic pyloric stenosis. The fluid found is practically a pure secretion of the gastric tubules. We have been fortunate enough to observe 2 cases in which we could prove an active secretion in the fasting case. In 1 of these cases 130 c.c. of pure watery secretion was removed. After five minutes another 30 c.c. of clear aqueous liquid was extracted, and thereafter every five minutes 30 c.c. of the same liquid clear material was aspirated. This was observed for a half hour, whereupon our observations ceased, though the fluid was still being produced. The material withdrawn was free of biliary and pancreatic regurgitation, as evidenced by its color and freedom from pancreatic ferments, and free of saliva, the patient being watched and instructed to expectorate all fluids accumulating in the mouth. In this case at least a definite rate of flow was observed; 30 c.c. every five minutes, or 360 c.c. an hour. If continued for twenty-four hours in the fasting state this

would have meant 7344 c.c. per day. During the digestive periods this rate of flow would probably have been much accelerated.

We have attempted to collect fasting secretion in many patients not suffering from hypersecretion, by similarly emptying the residue and then watching every five minutes for evidence of normal secretory activity, but could never collect more than 1 or 2 c.c. of viscid material in such an interval.

The acidity of the fasting contents in hypersecretion shows the same range as normal cases, free acid ranging from 0 to 94 per cent., average 30 per cent.; total acidity from 10 to 100 per cent., averaging 52 per cent. The acid titer of the fasting stomach is usually lower than the acidity at the height of digestive activity, but is usually of the same titer as is the fluid produced in the postdigestive hypersecretory phase. The titer of the fasting contents is the titer of the gastric secretion of that individual stomach for the whole of the twenty-four hours except for the short periods in which digestive activity is at its maximum.

Ewald Test-meal. The most important factor to be determined is the total amount withdrawn. This varied between 10 c.c. (achylia gastrica) and 325 c.c. as a maximum. The average amount was 102 c.c., a figure decidedly above the normal. The proportion of fluid to solid food residue (starch) was always from 4 to 1 to 10 to 1, indicating a large increase in the secretory quotient. The acidities were for free acid an average of 35 per cent., for the total acid 64.3 per cent.

Fractional Test-meals. It is with the fractional test that the greatest information is derived. The curves were observed (quarter-hourly) for from two to six hours, after the ingestion of the gruel. As the emptying time was not materially different from the normal standard, practically every period after two hours (or two and a quarter hours) represents a pure hypersecretory phase. The duration of the observations in most of the cases was limited only by the time at the convenience of the observer and the fortitude and indulgence of the patient. Most of the cases observed four, five and six hours were secreting just as strongly then as at the beginning and gave every indication of being cases of continuous hypersecretion. On the other hand, after the two- or three-hour period some of the cases seemed to wane, and some to come to an end, with a gradual fall of the acidity curve. These were examples of alimentary hypersecretion. Between 50 per cent. and 60 per cent. of the cases gave every indication of being of the continuous type. This is a rather striking figure in contrast with the idea of Reichmann, Riegel and others, who regarded continuous hypersecretion as a very rare phenomenon. It is probable that some or many of the cases regarded here as alimentary would also have fallen into the class of continuous secretion had they been observed for a longer period.

The maximum height of free acid in this series of fractional tests

ranged from 0 to 114 per cent., but averaged 69.2 per cent. The maximum titer for total acidity varied from 14 per cent. or 20 per cent. in very few cases, to 140 per cent. in extreme types. The average for all cases was 84 per cent., but the number of cases titrating between 100 and 136 was 16 out of a total of 68 curves studied. From these figures we readily surmise that hyperacidity and hypersecretion are close concomitants, though not necessarily so. The type of the curve is of more interest than the height or altitude of acidity reached. The curve in most cases shows two phases: a primary or digestive phase, following rather closely the usual digestive curves and showing a tendency to return toward the base line at the end of two hours (emptying time); and a secondary curve, characterized by a slight secondary rise until a certain level is reached. This level is maintained with very little variation for hours and hours. The level sought by any individual is personal to that individual; some stand steady at 40 per cent. for total acidity, some at 50 per cent. or 60 per cent. and a few still higher. Such an illustration is seen in Chart I, representing a case of pyloric ulcer with a mild grade of pyloric stenosis present. The secondary phase is established at 50 per cent. acidity.

Pathologic physiology has emphasized the supreme importance of motility and emptying time in the stomach.

In cases of pure hypersecretion without evident organic disease there is no change from the normal standard of motility. Occasional exceptions will be noted later. The presence of a pyloric or peripyloric ulcer introduces another and a mechanical factor, often coexistent with the hypersecretion. In the presence of organic disease, delay in motility can safely be attributed to the pathologic process. In a large number of this series where no organic disease was suspected a normal emptying time existed in the presence of marked hypersecretion.

The Clinical Diagnosis in Cases of Hypersecretion. The cases in this series were grouped under the following diagnoses.*

TABLE I.

Duodenal } ulcer	13
Gastric }	
Carcinoma of stomach	3
Carcinoma of common bile duct	1
Cholelithiasis	2
Gastric neurosis	19
Syphilis, tertiary	3
Syphilis, tabetic crises	1
Migraine, neurosis	2
Spastic colitis, neurosis	2
Asthma	1
Achylia gastrica	1
Chronic appendicitis	5
Tuberculosis of kidney	1

* In four of these cases a diagnosis of concurrent duodenal ulcer and chronic appendicitis is made.

It is readily observed that hypersecretion is a symptom, common to many diseases and conditions, and pathognomonic of no single one.

In order the better to appreciate the factor of hypersecretion in the various types of maladies let us consider a few illustrative cases with their corresponding chemical data.

Chart I illustrates the fractional curve of a case of pyloric ulcer with a moderate degree of organic pyloric stenosis. The patient, an adult, male, aged forty-five years, had suffered epigastric cramps for two years. All food produced abdominal discomfort, eventuating in cramp-like pains one and a half to two hours after eating. Nausea and repeated vomiting supervened during the last five months. The fasting contents of this patient amounted to 130 c.c., no food residue being present. One hour after an Ewald test-meal 200 c.c.

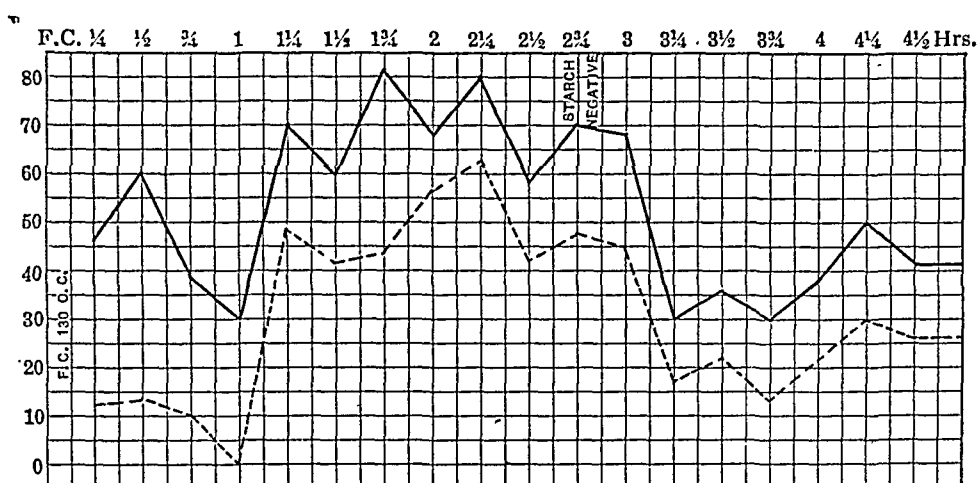


CHART I

were removed, having a free acidity of 55 and a total acidity of 88 per cent. Vomiting of large amounts of food was observed, up to 1000 c.c. being noted on one occasion. At operation a hypertrophied and thickened pylorus was palpated, adjacent to which was a large inflammatory mass adherent to the head of the pancreas.

The curve of this fractional test was typical both of a gastric or pyloric ulcer and of hypersecretion. The rise of acid was gradual and sustained reaching its height only at the one and three-quarter hour period and sustained to the third hour. The last trace of starch left the stomach at two and three-quarter hours, a definite delay from the normal. Subsequent to this emptying of the stomach there was a fall of acidity to a level of 40 to 50 per cent. total acidity, at which point the hypersecretion continued indefinitely; this hypersecretion consisting of clear watery fluid continued uninterruptedly up to the last observation which was made five and one-quarter

hours after the ingestion of the oatmeal gruel. We observe here a prolonged and sustained digestive cycle with a maximum acidity between 70 per cent. and 80 per cent. and a secondary stage of supersecretion lasting indefinitely thereafter, though maintained at a constant though lower level of acidity. This case may well have been accounted as one of Reichmann's disease, for it bears all the clinical characteristics of such, as, for instance, abdominal pain, acid eructations, vomiting of very large amounts of fluid, loss of weight, excess of material in fasting contents and continuous secretion of the stomach at all times throughout the day.

Yet it was a case proved at operation to be one of peripyloric ulceration.

Chart II is an illustration of an instance of exaggerated hypersecretion, accompanying most likely a gastric or duodenal ulcer.

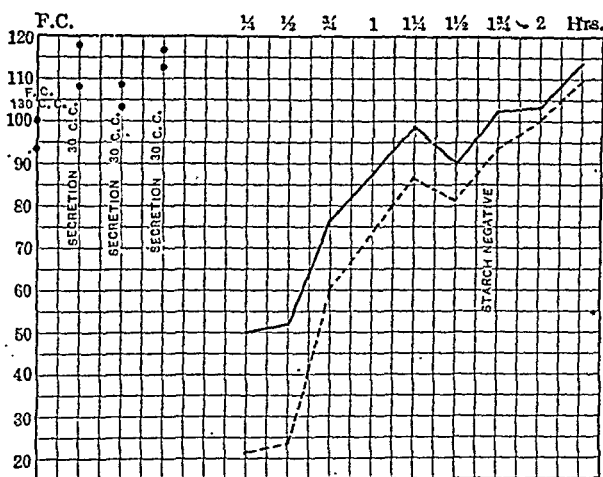


CHART II

During the last two years the patient had suffered with recurrent attacks of belching, heartburn eructations and constipation. The attacks were separated by intervals of three to five months of well-being. During the attacks copious vomiting took place, usually a few hours after eating, the vomitus being occasionally brownish-black in color. Stools were dark brown, but never absolutely black. On one occasion we were able to wash from this man's stomach skins of prunes eaten thirty hours previously.

The fractional chart shows that 130 c.c. fasting contents containing food were obtained. Thereafter (still in the fasting state) every five minutes 30 c.c. were removed, consisting of clear watery fluid and representing pure continued secretion in the fasting state. The gruel test-meal followed and demonstrated a condition of marked hypersecretion. The last gruel left the stomach at the

one and three-quarter hour period; following this we note another period of continuous gastrosuccorrhea, the observations being interrupted by the fatigue of the patient. The level attained by the gastric supersecretion was unusually high, reaching between 120 per cent. and 130 per cent. at the last observation.

We note that the level of acidity in this case in the empty or supposedly resting state is far different from that in the preceding one (Chart I), the resting level here being about 120 per cent. while in the previous one it is 40 to 50 per cent. We have observed many cases of ulcer in which the level of the supersecretion lay between these two extremes. The height or average altitude of acidity is no index of the disease and no level can be said to be characteristic of ulcer. Every person may be said to have his or her average level, common to that person both in health and disease.

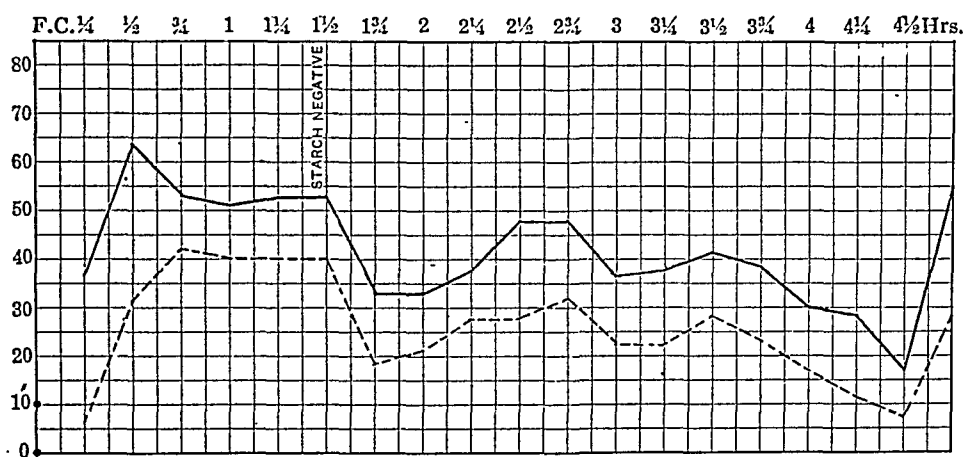


CHART III

The following case was one of a neurotic nature, with some evidence of mild disease process in distal organs. He suffered from an inactive pulmonary tuberculosis; he had complained for eight years of vague generalized abdominal pains and occasional attacks of diarrhea. He was of a neurotic temperament, easily frightened and irascible. A simple chronic granular proctitis and sigmoiditis was present. His gastro-intestinal roentgen-ray examination was negative. The chart (Chart III) of this case was typical of a continuous hypersecretion with low, titrable acidity; the primary digestive phase lasted only one and a half hours and was followed by a typical secondary continuous supersecretion lasting up to four and three-quarter hours, the observation being interrupted because of the fatigue of the patient at this point.

Chart IV illustrates the fractional curve in the case of an adult male suffering for four weeks from nervousness, sleeplessness, heavy

sensation in abdomen, loss of appetite and constipation. This was evidently an example of psychoneurosis with some abdominal symptoms. The chart was one of typical hypersecretion, there being a constant outpouring of abundant clear fluid in all the fractional tubes examined. Motility was normal.

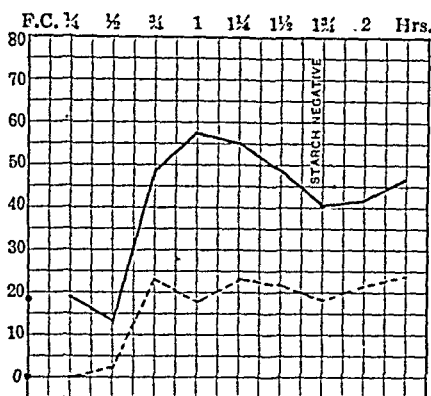


CHART IV

The hypersecretion present here was probably part of a general neurosis; hyperstimulation of the vegetative nervous system was manifested in many of his clinical symptoms.

The next case (Chart V) was that of a man, aged sixty-seven years, who had been under observation in the hospital on and off during

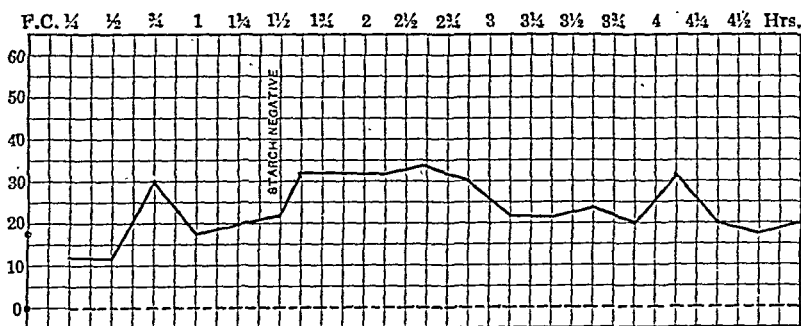


CHART V

the last five years, suffering from constant pain in the epigastrium referred to the precordium, worse in the fasting state. Generalized pruritus was present, as well as chronic constipation.

Chart V showed a condition of anacidity accompanied by a marked hypersecretion. The emptying time was one and a half

hours, yet when observed up to the four and three-quarter hour period this stomach was freely secreting a limpid fluid containing no free acid and a total acidity about 20 per cent. Only a few cubic centimeters of fasting contents could be obtained in the morning. There was present in this man a functional disturbance of the gastric secretion probably of a neurogenic origin.

Chart VI represents a similar case in a middle-aged female, with exaggerated subjective gastric symptoms. Thorough observation over several weeks failed to reveal the presence of organic disease. The fractional curve was one of complete anacidity (ferments faintly present) with a prolonged hypersecretion.

It is impossible to differentiate in such a curve the hypersecretory from the digestive phase.

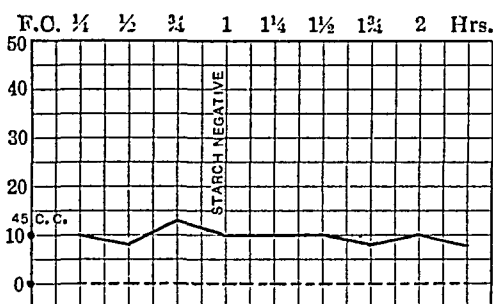


CHART VI

Cases 2 to 6 inclusive are examples of gastric neurosis with functional hypersecretion. The emptying time was normal in all, the range of acidity from complete anacidity to hyperacidity. Hypersecretion is the one common factor being present throughout, independent of the range of the acid titer. Vomiting was not present in these cases, nor were any large amounts of fasting contents obtained on repeated examinations. They are more in the nature of alimentary hypersecretion (hyperpepsia of Hayem) though some of them partake also of the character of continuous supersecretion (gastrochronorrhea of Hayem).

The next example is illustrative of a case of late syphilis, with 4-plus positive Wassermann reaction. Organic disease of the stomach was lacking, radiograms showing only ptosis with normal gastric contour. The Wassermann reaction in the spinal fluid was similarly 4-plus, though no clinical evidence of syphilis of the nervous system was present. The fractional curve, Chart VII, was typical of that of continuous hypersecretion; emptying time normal two and a quarter hours, followed by an enduring phase of pure hypersecretion observed up to four and a quarter hours.

Syphilis was present in 4 of the 50 cases studied and was an important factor etiologically.

The following 2 cases, Charts VIII and IX, were instances of general neurosis, accompanied by chronic migraine and frequent attacks of vomiting, often of large amounts of fluid. The malady extended in both cases over a large number of years.

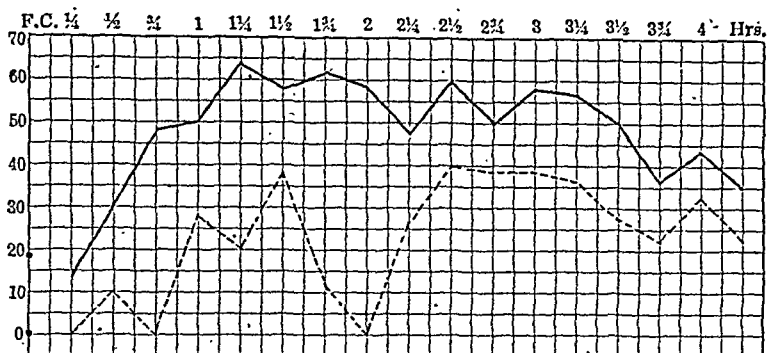


CHART VII

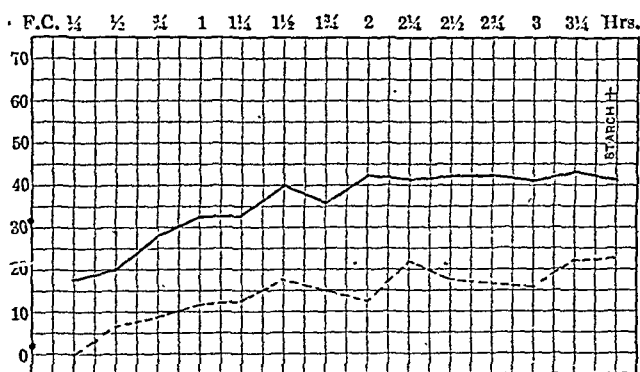


CHART VIII

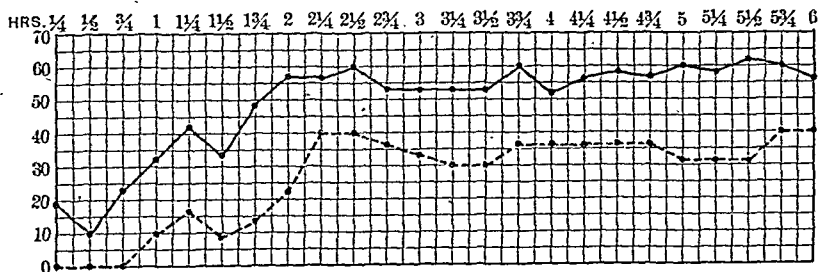


CHART IX.

A definite delay in motility was observed in both cases. In Chart VIII we note that at three and a half hours starch (oatmeal

gruel) was still present in the stomach; in Chart IX starch was visible *at the end of six hours*. In this latter case organic disease at the pylorus was so strongly suspected that operation was advised. Laparotomy revealed a patent pylorus, easily admitting two fingers and no evidence of organic malformation. In this group we have hypersecretion accompanying the symptom-complex of migraine and associated with a definite delay in gastric motility. Pylorospasm is here probably the primary gastric factor, the hypersecretion being due to the prolonged stay of the food in the viscus.

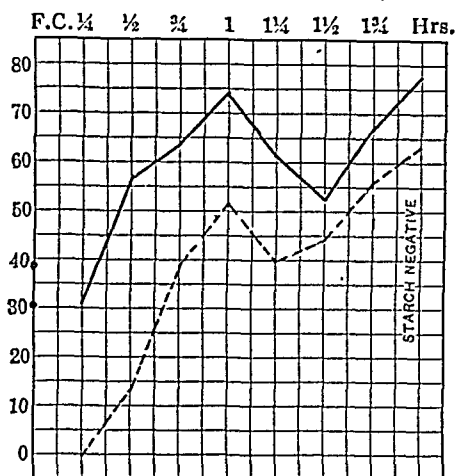


CHART X

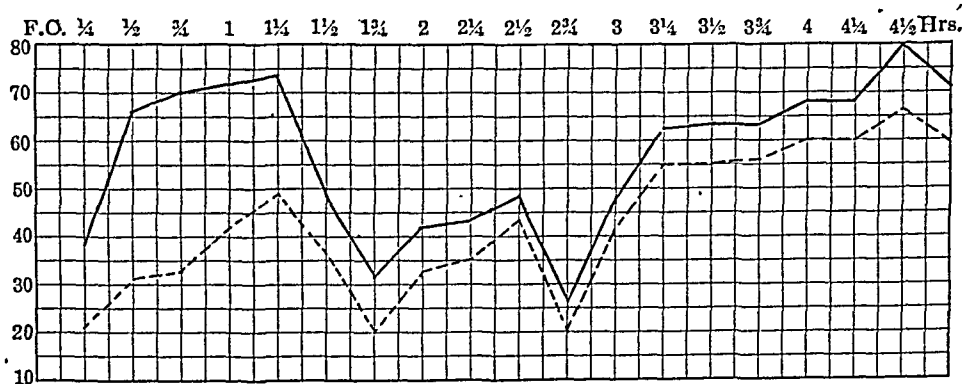


CHART XI

What relationship exists between hypersecretion and the various clinical pictures with which it is associated? A reference to Table I will show that it is associated with no single clinical complex or disease. It exists as a frequent concomitant of gastric and duodenal ulcer, more particularly of the former. As such it is often associated with delayed motility due to pylorospasm or pyloric stenosis (5 out of 13 cases), while in another larger group (7 out of 13 cases) motility was normal and yet hypersecretion present,

If to this group we add the 3 cases of carcinoma of the stomach with hypersecretion, we have 16 cases of gastrosuccorrhœa apparently due to protopathic or intragastric irritative stimulation. Many of these cases were rather typical of the syndrome of Reichmann's disease as he first described it in 1882. It is quite probable that in the early literature all cases of Reichmann's disease were cases of pyloric ulcer or pylorospasm from gastric or duodenal ulcer. Among these 16 cases of organic disease of the stomach is a fair number showing only limited degrees of hypersecretion (alimentary hypersecretion) and not developing at any time the *continuous* magensaftfluss and copious vomiting of the Reichmann syndrome. Further we know from our own statistics published in an earlier paper²¹ that only 30 per cent. of all gastric or duodenal ulcers show hypersecretion. Thus we may draw the conclusions that organic disease of the stomach (ulcer or neoplasm) explains only about one-third of the cases of hypersecretion.

In the next group we can place 2 cases of cholelithiasis and 3 cases of chronic appendicitis, all with reflex gastric symptoms. These form a very well-defined group. In the 3 cases of chronic appendicitis, with irritative symptoms perfect health and function was restored after the removal of the appendix. These 5 cases, together with a case of carcinoma of the common bile duct, constitute 6 cases of organic disease in neighboring organs with reflex gastric hypersecretory phenomena.

The type of curve in these cases was more in the nature of alimentary hyperpepsia than modelled after the chronic supersecretive type. This group represents extrinsic gastric stimulation of organic and abdominal origin.

The remaining cases fall into a final group. They produce their irritative hypersecretory phenomena through the nervous regulatory apparatus of this important secretory viscus. There seems little doubt that psychical influences play an important role in many of these cases. Thus in two of the cases included in this series, "bad news" initiated the subjective gastric phenomena.

In another case, one in the hospital ward being treated for asthma, an interesting observation was made. He was a young male adult suffering for many years with attacks of asthma occurring at irregular intervals. He complained, in addition (during the last four months), of severe abdominal cramp-like pains in the right hypochondriac region, referred to the back. Vomiting occurred on an average of once a week and gave relief from subjective symptoms. Heartburn set in usually fifteen to thirty minutes after a meal.

During the earlier part of the stay in the hospital the asthma was not severe, in fact almost unnoticeable. The patient was given a Sippy diet in an attempt to control subjective gastric symptoms.

The curve before instituting the diet showed a rising and sustained curve, slight hyperacidity, motility normal. During the

first ten days of restricted diet the patient reported progressive improvement; on the tenth day the patient became excited over the administration of a dose of Epsom salts for constipation. He felt convinced that the cathartic had harmed him and injured his treatment. During his excitement a severe attack of asthma set in. A fractional test which had been ordered for the same morning showed a marked hypersecretion of the most typical continuous type (magensaftfluss). Specimens were obtained up to four and three-quarter hours after the ingestion of the meal and the profuse limpid fluid flowed freely.

This incident is cited to indicate the rôle that powerful psychic irritation plays in the control of secretory regulation in the body. Pawlow and Cannon have emphasized the influence of fear, anger and other excited emotions on the gastric secretions. In the experimental studies on animals inhibition of secretion was more common. In this clinical case there is evidently a direct central nervous system stimulation with apparent radiation down the stimulatory fibers of the vagus, inducing probably both the asthma and the gastric hypersecretion (parasympathetic path).

It is comprehensible that most of the cases in the group of "neuroses" bear an analogy to this the above incident. For in them there is a constant nervous overexcitation. Bad news from home or an irritating incident serves only to exaggerate the type of the case.

Organic nervous disease may and does cause the same symptoms. Tabes has long been recognized as an etiologic factor in periodic gastrosuccorhea (von Leyden). Tumor of the brain may do the same as well as hysteria. This is the group classed by Reichmann and accepted by successive writers as "periodic continuous hypersecretion," that is hypersecretion present during the attacks or crises of the nervous malady and absent in the remission periods. The clinical picture termed by Rossbach "gastroxynsis," is only another subspecies of this same group; it consisted of attacks of vomiting of copious amounts of fluid associated with headache and crises of nervous or hysteric character.

The curves obtained in the cases of migraine were remarkable not only for the presence of hypersecretion but because of the very prolonged emptying time of the organ. There is evidently a powerful nervous stimulus, irradiated along both motor and secretory nerves of the organ, inducing motor pylorospasm and secretory hyperstimulation. As a clinical picture pylorospasm as a result of organic disease of the central nervous system is well recognized as an accompaniment of tabes, brain abscess or brain tumor. The stimuli reaching the stomach in the above-cited cases of migraine are apparently of analogous, though not identical origin. We have established hypersecretion as occurring then, in three groups of cases:

1. Organic disease of the stomach, particularly ulcer (intrinsic origin).
2. Organic disease of associated abdominal organs (reflex action).
3. Hyperirritable conditions of the cerebral or autonomic nervous system, both organic or psychic (extrinsic origin).

Does hypersecretion ever occur in normal individuals? Rehfuß²² has expressed the opinion that hypersecretion does occur occasionally in individuals in a state of perfectly normal health, and cites an instance in a group of students studied as normal controls. He reiterated this opinion quite recently in a paper²³ read before the American Gastro-enterological Society last year. Yet the large number of control cases cited by him in his series, as well as those of Fowler and Zentmire,²⁴ and our own controls, numbering many hundreds in hospital cases observed for all varieties of ailments, denies the point that hypersecretion is a normal phenomenon or occurs more than as a great exception in persons entirely devoid of organic or psychic stigmata. It is just as likely that the occasional so-called normal individual upon whom a control test is made is really a potential psychoneurotic or vagotonic. It may be argued that all of our studies have been on chronic hospital cases or cases actively complaining of well-defined symptoms. Still we answer that in the hundreds of cases observed with a functionally normal digestive organ the stomach empties itself promptly at two hours, and thereafter no further secretion is obtainable. All cases varying from this standard by showing digestive or post-digestive hypersecretion are regarded as suffering with a functional aberration from the normal secretory standard of health.

In the light of the studies made upon this series of 50 cases, closely observed and studied, let us review critically the clinical literature of the last twenty-five or thirty years on the subject of hypersecretion. Does Reichmann's disease exist today as an independent clinical entity? This is best answered in the negative. Practically all the cases described by Reichmann^{2 15} and Riegel,^{4 9} Strauss,¹¹ and others were typical instances of ulcer complicated by continuous hypersecretion. Soupault operated upon 58 cases of so-called Reichmann's disease and found ulcer in all of them.

But continuous hypersecretion as a symptom does exist, not as an independent disease but as one symptom, usually a secondary symptom, of other diseases, organic or neurogenic.

All the clinical symptoms of Reichmann's disease, such as pains, vomiting, pyrosis, loss of weight and continuous hypersecretion may be seen associated with various clinical conditions other than peptic ulcer.

The group of periodic hypersecretion stands today in an unmodified and strong position, as originally described by von Leyden,²⁵ Rossbach,⁶ Moebius²⁶ and others. The hypersecretion is not the

disease but is the secondary phenomenon of a malady of the cerebral nervous system.

What can we say of digestive or alimentary hypersecretion, as revived by Strauss,¹¹ and discussed by Calvo and Zweig,²⁷ etc? Many of these writers attempted to associate all hypersecretion with ulcer. We see from the data in this series of cases that they claimed too much and that barely a rough 33 per cent. can be so classified.

It may not be amiss to discuss the nervous mechanism by which an abnormal secretory activity of the gastric acini is produced. The stimulatory fibers to the glands of the stomach are regarded as being in the parasympathetic system or the pneumogastric nerve; inhibition of secretion rests with the sympathetic system whose neurons lie in the celiac plexus. The extrinsic motor control follows in general the same routes. Abnormal stimuli originating in other nervous ganglia of the abdominal plexuses are referred or reflected along the vagus system, producing exaggerated peristalsis, pyloric irritability and pylorospasm and supersecretion. This is termed by Head and Pottenger²⁹ a viscerosensory reflex. The close association between vagotonia (Eppinger and Hess³⁰) and most of these cases of hypersecretion is worthy of attention. The relation of vagotonia to ulcer of the stomach and duodenum has been repeatedly pointed out (Petrin and Thorling³¹); one cannot overlook the possible sequence of vagotonia, hypersecretion and ulcer. Hypersecretion of long standing may conceivably induce ulceration, or, *vice versa*, the presence of an ulcer may cause, by intrinsic irritation, a sequential supersecretion.

The efforts of Nikolaysen³² to produce hypersecretion by pilocarpin stimulation of the vagus nerve were unsuccessful; his experiments are too few to warrant sincerely doubting the above-mentioned hypothesis.

There is reason to believe that adrenal insufficiency plays a role in this symptom, either through the thyroid gland or independently of it. The experiments of Finzi,³³ of Friedman³⁴ and of Mann³⁵ in the production of ulcers by adrenalectomy and pilocarpin injections are very suggestive along this line.

The question has often been raised by previous writers whether delayed motility was not accountable for the large amounts of fasting contents and test-meals removed in this class of cases. J. Kaufmann³⁶ has demonstrated in a typical case of Reichmann's disease that the predominant factor was a delay in motility due to ulcer. There is no question that in the cases of gastrosuccorhea of organic gastric origin, delayed motility plays an important and mechanical role. But in the remaining cases of this group, periodic and alimentary hypersecretion, no delay in the exit of food was demonstrable. Atony as a factor deserves today but little consideration, since normal emptying time is not inconsistent with a

well-marked atony. It is the opinion of the authors that delayed motility is not an essential or intrinsic factor in hypersecretion. It often accompanies gastrosuccorhea, but just as often, or more so, we note normal emptying time with exaggerated supersecretion.

The cases of migraine with markedly delayed motility are exceptions, but deserve very close notice because of the unusual and extensive degree of the motor insufficiency.

Treatment. The indications for the treatment of gastric hypersecretion are clearly laid down in the general principles of this paper. The importance of removing both extrinsic and intrinsic stimuli of an abnormal nature is self-evident. Restriction of diet is one of the basic principles; rest in bed is a necessary corollary of this treatment. In a series of cases of hypersecretion studied by the author and previously reported the effect of marked restriction of diet, both solid and fluid, was studied; 45 per cent. showed local improvement in the chemism of the stomach and 80 per cent. were discharged from the hospital free of symptoms. The use of atropin is warranted by experiments published recently.³⁷ We were able to demonstrate a striking reduction in the supersecreted fluid after hypodermic administration of this alkaloid. Less favorable results followed the administration by the mouth or over even longer periods.

The removal of abnormal nerve stimuli, whether of cerebral nerve system or of viscerosensory origin, is self-evident; no treatment that ignores the psychical condition of the patient will be effectual in a case wherein vagotonia is a factor or hysteria or a psychoneurosis is present.

Organic brain or spinal-cord disease once diagnosed, calls for its own treatment.

Summary. 1. Hypersecretion is a symptom; it is a functional disturbance of the secretory apparatus of the stomach. It is not a disease *per se*.

2. It is a frequent symptom, occurring most commonly in males, and being present in probably at least 10 to 15 per cent. of all persons with gastric complaints.

3. Its occurrence is independent of the acidity titer of the stomach; it is found more often associated with hyperacidity, but can be seen through all the grades of acidity, even in achylia gastrica.

4. Most of the cases of hypersecretion are of the continuous type, lasting throughout the digestive and interdigestive period. The most severe type of cases, when associated with vomiting, emaciation, thirst, epigastric pain, etc., constitute Reichmann's disease. These cases are nearly all due to gastric or duodenal ulcer (Intrinsic cause).

5. Of the milder grades of continuous hypersecretion (alimentary hypersecretion, without vomiting, etc.), many of the cases are attributable to ulcer (about one-third); the remainder are due to abnormal nerve irritation, either *reflexly* from abdominal disease in other organs or from neurotic instability, such as vagotonia, psychoneurosis, etc. (extrinsic cause).

6. A few cases are due to diseases of the cerebral nervous system, hysteria, psychic causes, etc. (intermittent hypersecretion).

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OBSERVATIONS UPON THE TREATMENT OF THE CHRONIC INTESTINAL INVALID.*

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I. INTRODUCTION. The object of the present paper is to record some of the more definite impressions which have resulted from a ten-year intensive study of the chronic intestinal invalid. In 1910, when this study was first undertaken, information of value in regard

* An address delivered before the Hartford Medical Society, May 17, 1920.

to this particular type of patient was conspicuous by its absence. No one knew, and few seemed to care, what was going to happen to a class of invalids who, if seldom seriously ill, were practically always physically if not mentally inefficient. The present study has been prosecuted in the operating room, in various pathologic institutes of Europe, in medical libraries, and finally, for the past five years, by means of practical experience in the medical treatment of these patients. Various aspects of this study have been referred to in published articles.¹⁻¹⁵

As a result of this work there has emerged from the haze of uncertainty a series of rather definite procedures, the application of which has resulted in the obtaining of a satisfactory percentage of improvement in the clinical condition of the type of patients under discussion and in their relative freedom from relapses. In a word the majority of the patients themselves have seemed satisfied with their new ability to carry on the daily affairs of life, and they have usually stated that this ability is in marked contrast to their previous years of physical and perhaps mental incapacity.

II. MENTAL AND PHYSICAL CHARACTERISTICS OF THE PATIENT.

If the *genus homo* is subdivided into four species on the basis of visible physical development, under the headings of hypersthenic, sthenic or normal, hyposthenic and asthenic, we may discover by even a little investigation that the hyposthenic species today is not only conspicuous in point of numbers on a percentage basis, but that especially in the United States, the percentage of individuals belonging to this hyposthenic species is steadily on the increase. There are doubtless many reasons for this state of affairs. Three possible reasons follow:

1. The reduction of infant mortality.
2. The national dietary.
3. Labor-saving machinery.

Weakling infants, as a result of the crusade for reducing infant mortality, are being kept alive in an increasing ratio. If saved through the period of infancy these children are frequently fed during their growing stage (assuming that the feeding is adequate from a calory point of view) on diets deficient in minerals, especially calcium. Later, when adolescent or adult these individuals are often saved from or prevented from acquiring adequate physical development by the increasing use of labor-saving machinery in all our industries. The result of this sequence of events may be predicted as surely for the human as for the dog, or any other organism depending upon an adequate use of its musculature for the adequate muscular development upon which its well-being depends.

The adult hyposthenic may present symptoms predominantly nervous, circulatory, orthopedic or gastro-intestinal. Obviously, any combination of these groups of symptoms may also appear.

It is the gastro-intestinal variety of the hyposthenic species of the

genus homo, with which the present paper is concerned, under the title of the Chronic Intestinal Invalid.

The chronic intestinal invalid usually comes to the physician complaining of digestive symptoms and general poor health. When the complaints of such a patient are examined in detail, however, it will be found that many of them are almost identical with those presented by the other varieties of the hyposthenic species, especially the so-called neurasthenic variety. In general the chronic intestinal invalid shares with the other varieties of the hyposthenic species two distinctions, if they may be called such. On the one hand a careful routine physical examination is usually reported substantially negative, except that the patient is in a state of general poor nutrition and more or less obvious fatigue. On the other hand, although well-marked pathology is lacking, the patient feels, often looks and usually acts sick. Furthermore, such a patient will most persistently continue to say that he is sick, and inefficient both mentally and physically, no matter how often he is assured by well-meaning physicians that there is practically nothing the matter with him, and that if he will only cheer up he will be all right. In this case it is usually the patient who is correct and not the physician.

From the mental point of view the most characteristic finding is a constant overreaction to stimuli of all kinds. Such patients are consequently in a state of perpetual mental unrest. This is reflected in their changeability, the impossibility of their doing prolonged concentrated mental work, and their customary difficulty in getting adequate restful sleep at night. This fundamental excessive irritability is also suggested by a poor or capricious appetite, vasomotor instability, frequent floods of tears, apprehension and suspicion. Nervous energy is being wasted at a terrific rate in all directions, with the unavoidable result that sooner or later physical rest is enforced by collapse. This may proceed to a state in which nausea and vomiting are almost constant. An excessive flushing of the face on the slightest provocation contrasts markedly with the pallor observed in repose. A false vivacity, a peculiar harsh tension of the voice, excessive nervousness, tachycardia, precordial pain, cold and moist extremities and excessive sweating from the axillæ singly or in combination often accompany a spastic constipation and a muddy skin. Yet a fictitious cheerfulness on the part of the patient does much to mask continual bodily discomfort and emotional hypersensitiveness and to throw the casual observer off the track in regard to the true state of affairs.

Physically the bones are usually long and slender and the musculature is nearly always deficient. On account of the absence of a normal amount of erector spinæ muscle the vertebral spines, instead of being inconspicuous in a furrow between the heavy back muscles, are perhaps the most conspicuous feature presented to the observer on inspection of the patient's back. Intimately connected with the

usual fatigue posture is the collapsed lower thorax, the greatly narrowed costal angle, and what might be called the "clam-belly" type of abdomen prominent below but not above the umbilicus.

On inspection the pupils are usually dilated. The respiration is rapid and usually of the upper thorax type. The skin is likely to be dry, often rough, and usually yellowish dirty brown in color. The subcutaneous tissue is lacking in fat, and being without elasticity, feels to light pressure like a wet rag as compared with the rubber sponge sensation obtained on light pressure of the skin of a normal person. The muscles themselves are small, and if they can be relaxed are of poor tone and as lacking in resilience as the subcutaneous tissue.

One of the most striking signs on examination, associated with the discolored and abnormal skin, is a marked dirty discoloration of the entire eye socket. This sign¹⁵ is so constant in its appearance in this type of case as to enable one to say almost at a glance that its possessor has some definite chronic intestinal difficulty; from experience it may be further said in connection with this eye sign that it often accompanies ileal regurgitation and is in itself a definite indication for diet. When diet is properly applied this eye sign and the muddy skin tend simultaneously to disappear.

Unless there is some infection about the teeth, tonsils or sinuses the general physical examination is usually reported negative. But local examination of the abdomen discloses a characteristic distribution of gas. On percussion it will be obvious that the gas is either generalized throughout the entire abdomen or limited to one of two locations. The more common of these locations is the region of the cecum and ascending colon. The second point of election for finding gas is in the sigmoid loop. Not infrequently, on careful palpation, one obtains a gurgling sensation of gas in the cecal region, suggestive of ileal regurgitation. Occasionally one may obtain a striking contrast on palpation between the size of the dilated cecum and ascending colon, and the rope-like spastic descending colon.

Locally such a patient complains of the classic symptoms of pain, gas and constipation. This pain is usually intermittent and associated with gas in the cecum or about the flexures. In addition there is another characteristic type of pain met with in the epigastric region, which, although simulating the pain of ulcer, is apparently largely connected with the narrowing of the costal angle, since it is permanently relieved simultaneously with the widening of this angle.

Gas formation is perhaps the most disagreeable feature of the situation, and in these patients one has to deal not only with the actual gas formation within the intestine but with an often considerable degree of inability to get rid of extraneous air swallowed with the food. When the intestinal tract is unusually spastic it is not infrequent to find that the patient has great difficulty in relieving

himself of gas in the stomach; if possible, it is with explosive effect. The same phenomenon holds true with regard to relief from gas in the rectum. The result is that although the particular patient may be manufacturing no more gas than his healthy neighbor, he is in much more constant discomfort on account of his inability to free himself from what gas is present.

A second point worthy of mention in considering the question of discomfort from intestinal gas is that when the tone of the intestinal musculature is poor the intestine is more easily distended by gas than normally, so that instead of there being a tendency for gas to move along in one direction or the other it remains in one place to the greater discomfort of the patient. This is especially true when there is a dilated cecum and ascending colon in conjunction with a spastic descending colon.

Constipation is for these patients almost normal. It is of one of two types, spastic or atonic. Except in unusual circumstances it will respond to proper treatment, so that instead of having to depend upon large quantities of irritating laxatives a reasonable degree of freedom from cathartics may be brought about by the use of laxative foods.

III. RELATION OF PHYSICIAN TO PATIENT. The relation of the physician to his patient, when the patient is one of the chronic intestinal invalids under consideration, presents certain contrasts to the conditions prevailing in the practice of acute medicine or surgery. In the practice of acute medicine the physician is called upon to see a patient who is presumably acutely ill from a definite disease. Consequently, in his analysis, the physician studying the acutely ill patient is likely to ask himself questions in somewhat the following sequence:

1. Is the patient sick?
2. From what disease is he suffering?
3. What can be done for it?

The physician's focus therefore is primarily upon a clinical entity, perhaps upon a self-limited disease of fatal intensity, and it is unavoidable that the seriousness of the disease may for the time obscure the individuality of the patient who presents the disease.

In the case of the chronic intestinal invalid the focus of the physician must be much more that of the family practitioner. It must be upon an individual who is not well. The patient has probably passed through a diagnostic mill, but may have yielded up almost negative findings. In spite of this the patient continues to complain of mental and physical debility. If the physician is human he must desire to help his patient. In order to throw light upon the obscure problem presented, the intelligent physician must begin his inquiry in somewhat the reverse order from that employed by his confrère who is devoting himself to acute medicine. Thus it is necessary to determine, first of all, with what kind of an individual

one is dealing and how he will react mentally and physically to his environment. The question of disease in this study remains almost always secondary to the question of the individual who is presenting the disease.

A second contrast between acute and chronic medicine becomes obvious when one considers that in acute medicine one clear-cut disease is usually diagnosed. In chronic medicine, on the other hand, the diagnosis is almost never single or simple. There is always a multiplication and a complexity of complaints. Possibly no one of these milder complaints would singly be of consequence. But in conjunction these mild disabilities may come to reach a sufficiently formidable total to prostrate the hyposthenic patient.

The chronic intestinal invalid may temporarily look, comparatively speaking, so well that no one will believe him to be sick. As a result he may get very little sympathy. Since he is exceedingly sensitive to injury, such a patient gradually learns to avoid giving strangers a chance to injure his feelings by the utilization of a mask of cheerfulness. It is impossible for the physician to begin to understand such a patient and to begin to learn with what material he must eventually deal in planning his course of convalescence until he has penetrated this defensive mental mask with which the invalid protects his hypersensitive feelings. For the purpose of penetrating this mask and arriving at an understanding of what is going on behind the mask the principal factor is time. The tenacity with which the patient will continue to remain protected by his mask (then suddenly coming out into the open as a hermit crab leaves his shell) is often amazing. For this reason it has been found desirable, when possible, to devote all the time necessary to the penetration of the defensive mask before the close of the first session with such a patient if real progress is to be obtained. On the basis of experience it may be stated that the penetration of this mask requires in proportion to the grade of mentality of the individual under consideration, anywhere from fifteen minutes to two or three hours. The result obtained, however, more than justifies the effort involved, for once such a patient is convinced of the reality of the interest of the physician in his personality and in his troubles, secrets no longer exist. The physician becomes at once friend, comforter, confessor. The necessity for arriving at this point as rapidly as possible is obvious when one considers the multitude of small details in the daily life of the patient, encompassed in the word environment, which may act to speed up or retard progress toward health.

IV. DIAGNOSIS. The diagnosis in these cases is always a complex of social, mental and medical factors. Thus although the principal complaint which brings the chronic intestinal invalid to the physician may be of a gastro-intestinal nature, one not infrequently may find that industrial fatigue has been a predisposing factor in producing malfunction of the digestive system. In such a case relief of the

gastro-intestinal condition may be impossible without readjustment of the hours of work and the hours of rest. It is always a case of Mohammed and the mountain. But usually it is possible to readjust the patient or the work, or both, in such a manner that slow but continuous progress toward health is realized. There is no doubt that, if possible, it is often more desirable to perform such an adjustment than to remove the patient from all work, the mental effect of this removal being bad both upon the patient and his family if, as usual, there is a family.

The importance of considering the mental factor in arriving at a diagnosis has been referred to in a recent paper.¹² It is indicated also in an interesting recent article by Patrick.²¹

A third predisposing class of factors of very considerable importance in the production of gastro-intestinal disorders are the concomitant but not infrequently neglected medical abnormalities such as those recently reviewed by Bastedo.¹⁶ It is, for example, not at all uncommon to find that mild orthopedic factors have been overlooked on account of the importance attributed by the patient to his gastro-intestinal symptoms. With women in the industries it is surprisingly common to find mild or even more serious degrees of abnormality of the generative functions as a background for digestive complaints. Thus, in one recent case, a telephone operator, aged twenty-five years, was referred for marked digestive troubles. She felt that her digestive troubles caused her nervousness and had convinced her previous physician to this effect. On careful inquiry it appeared that this girl had for years suffered from a very considerable degree of dysmenorrhea for about three weeks out of every four. She had previously mentioned this casually but had dismissed the matter as something that could not be avoided. It was possible, in the course of two or three months, to produce a very great improvement with regard to this dysmenorrhea so that pain only incapacitated her for two or three days. Parallel with this improvement came a marked improvement in the digestive conditions, and when last heard from the patient was back at work on full time.*

For the reason that apparently irrelevant details may prove of such importance as factors in treatment it is essential to devote unlimited time to the taking of a most complete history. It is perhaps not too much to say that with the majority of gastro-intestinal invalids an adequate history and a careful inspection of the patient may suffice to enable one to outline a reasonably successful plan of treatment, a treatment which in a considerable percentage of cases may lead to improvement in the patient's condition sufficiently marked to approximate cure.

* One year after beginning treatment, patient had just reported herself as cured. She has no longer constipation or digestive irregularity, and is for the first time in her life absolutely free from dysmenorrhea.

In general one may state, without danger of contradiction, that careful search will locate the primary etiology of very many cases of chronic intestinal disability in some focus outside the gastro-intestinal tract. This statement is but an amplification of the well-known remark that the stomach acts as a flag station for trouble in other portions of the gastro-intestinal tract far more often than it is itself primarily involved by pathology. Such etiologic foci will be found on search, in some of the other systems of the body, or in purely environmental conditions, reacting upon the patient through his impressionable mentality. A familiar example of this statement is the fact that in the laboratory one may cause a delay of almost an hour in the emptying of the stomach of a cat merely by allowing a dog to bark once or twice in the room in which the cat is being examined. It is thus evident that although the actual distress caused the cat by the dog was very temporary, the gastro-intestinal tract of the cat did not resume its normal function for a considerable length of time after the cause of the mental commotion had been removed.

V. TREATMENT. Rational treatment for the adult chronic intestinal invalid begins with preventive medicine in the child and in the adolescent intestinal invalid, since in probably 90 per cent. of all cases the defective gastro-intestinal tract and the unstable nervous system are conditions inherited rather than acquired. Unfortunately insufficient attention thus far has been paid to these patients during their developmental stages of growth, with the result that all cities and all hospital clinics provide for consideration large numbers of adult chronic intestinal invalids.

The active treatment of the adult chronic intestinal invalid divides itself into the early, intermediate and late phases of convalescence. There is, however, one underlying objective which must never be forgotten. This objective is the increased resistance of the patient to fatigue, and this increase in resistance to fatigue applies equally to the bodily and to the mental spheres. It is frequently necessary to build up from almost nothing the locomotor apparatus of the patient so that it will resist the ordinary strains of life. Simultaneously one must reduce, by educational and reëducational procedures, the overreaction of the nervous system to all forms of incoming stimuli.

During the early phase of convalescence it is frequently necessary to prescribe both internal and external rest. This period of complete rest is, however, usually of exceedingly short duration, since it is found that most patients do better at home rather than in a hospital, and with a definite if regulated degree of mental occupation and physical exercise.

The intermediate phase of convalescence is perhaps the most important. During this period, extending in time over one or two months, there must be an exceedingly careful gradation of physical

effort, so adjusted in length of time and so broken by frequent brief rest periods that in spite of the strains to which the patient is being put, one may obtain slow but gradual improvement in the condition of the general bodily musculature. During this intermediate phase there also comes a transition in the dietary from a somewhat limited soft and bland diet to one containing a larger variety of foods. One may also then introduce into the dietary the coarser foods which, if used earlier in convalescence, frequently result disastrously. In practice it has been found desirable to see ambulant patients twice weekly until the close of the intermediate stage of convalescence. A total of some twenty to thirty hours has usually been expended in personal attention to the individual chronic intestinal invalid by the time the intermediate phase is drawing to a close, and before such a patient begins, so to speak, to be able to navigate alone.

What is referred to as the late phase of convalescence is the period of time extending from the second or third to perhaps the eighth or tenth month after the patient is first seen, and from then on for perhaps two or three years. This is really a prolonged experimental phase during which the patient is enabled to find out, under occasional control, the precise extent to which he may, during his future life approximate what is called a normal standard of daily work with some prospect of being able to withstand it permanently, free from the specter of ultimate prostration. It is obvious that even the strongest individual may be broken by a sufficient amount of work. The object under consideration is, however, to determine how nearly normal an amount of work, a somewhat subnormal individual can accomplish without breaking. Once the high limit has been reached such an individual must realize that except for brief periods, under exceptional provocation, he can only exceed his limit under penalty of a definite danger of producing a recurrence of his symptoms. It is possible, however, during the progress of convalescence, to teach the patient methods by which, should he be forced to excessive efforts by family or other unavoidable calamities, he can, in the majority of cases, as soon as the excessive strain is over, work himself back without technical aid to a reasonably normal condition.

There are five distinct factors of fundamental importance in treatment; they are usually utilized in the following sequence:

1. Social.
2. Mental.
3. Dietary.
4. Orthopedic.
5. Glandular.

If one desires proof of the individual efficiency of these five independent factors they may be employed scientifically in consecutive sequence, so that in three or four weeks all five factors are being

simultaneously employed. It will be noted that of five factors fundamentally important to successful treatment only one applies directly to the digestive tract, 80 per cent. of all treatment utilized being therefore directed to objectives outside the gastro-intestinal system of the chronic intestinal invalid.

The necessity for considering the social status of the patient, not only with relation to character and hours of work but also with regard to the thousand and one other details which make up his daily life, is so obvious as scarcely to require mention except for the fact that it seems often overlooked. But frequently the first stage in relieving a patient of digestive symptoms may be the regulating of his hours of work, and a statement of the maximum length of time allowable for work, between rest intervals which must at first be passed in so far as possible in an absolutely prone position. Not less frequently nothing can be gained without modifying family friction or financial distress.

The mental factor has been referred to.¹² The methods of attack may be variable, but the result to be obtained is clearly a decrease in the overreaction of the patient to incoming stimuli of all kinds. One method used as a routine in the development of neuromuscular control is a system of very slow exercise,^{10 13} which often acts as a kindergarten course in mental reëducation for the patient.

The dietary employed is based in part upon a consideration of the large amount of work by reputable investigators, which tends to prove the ease with which the intestinal flora can be changed by a modification of diet; also, upon a consideration of the fact that ileal regurgitation is an exceedingly common finding in the chronic intestinal type of invalid. Ileal regurgitation was, for instance, demonstrated in 80 per cent. of a consecutive series of 50 chronic intestinal invalids.¹⁵ Eggs, meat and fish, as being potentially putrefactive, are at first absolutely excluded from the dietary, and the use of milk is restricted to the amount ordinarily employed in cooking. After a few weeks of complete restriction of the above foods it is very common to find that the patient's skin is distinctly less muddy. Slowly the yellowish color of the skin is replaced by white and then by pink, a transition which is greatly appreciated by the average woman patient. During this period of marked restriction of the diet, bran and the coarse vegetables are eliminated. No diet list is given, the patients being thus required to use their own brains in the working out of a suitable dietary. One advantage of this system is that the patient gradually acquires an adequate dietary for which he has the least possible dislike. If the dietary actually employed by the patient is written out and continually checked up at successive visits the results seem better from the point of view both of interest of the patient and of the physician than if a diet slip is handed the patient at the first visit. Eggs, meat and fish are rigidly excluded from the diet for at least one month. During the

latter part of this month, however, there is an increasing use of egg as a flavoring, in puddings or other cooked dishes in which the egg is finely divided by mixture with starches or the various vegetables. Meat gravies as relishes precede the use of meats as such. During the month of restricted diet liberal use is made of two special articles of food in conjunction with the usual fruits, starches, vegetables and fats. These two articles are cream cheese (or perhaps the ordinary cheese when used as a flavoring in various cooked dishes) and gelatin. The frequent use of flavored gelatins in the form of salads or desserts is encouraged. The necessary minerals, and the water and fat soluble vitamins, are provided for by the use of raw fruit and green vegetables and a good grade of butter. In this connection it is surprising to discover how few people are acquainted with the virtues both from a financial and an economic point of view, of chopped raw cabbage. This food as a salad with French dressing has been taken time and time again without the slightest discomfort or after-effects by patients who had previously stated that they could not possibly eat such a coarse vegetable.

At the end of a month or six weeks, if the progress of the patient justifies it (as evidenced by decreased constipation, lessened irritability, lessened disturbance from gas, better appetite and sleep, better color of the skin and fewer headaches) meat is put back into the dietary at first once a week. The intervals between the days on which meat is used are thereafter shortened according to circumstances. But in this type of case it has been found most unusual, if meat, eggs or fish as such can be handled with comfort more frequently than two or three times a week. The intermittent use of eggs, meat and fish has another virtue in addition to its economy and its tendency to discourage the growth of undesirable intestinal flora. If the patient has only to wait over one or two days of restricted diet before being allowed a day of full diet there seems to be much less desire for large quantities of these potentially putrefactive foods, which are handled with difficulty certainly in all patients with demonstrated ileal regurgitation.

An orthopedic factor requiring treatment is almost always present in the chronic intestinal invalid. Development of the skeletal muscles, and especially of the muscles responsible for the maintenance of correct posture, is considered a part of the daily routine in treatment. Although it would seem obvious it appears often forgotten that if a patient is not endowed with more than average viscera these somewhat mediocre viscera are certain to function better when given maximum opportunity by proper posture and muscle support than when they are compressed, as in the ordinary fatigue posture presented by these patients when first seen. The slow type of exercise previously referred to has the double virtue of being useful both from the mental and the orthopedic points of view.

During recent years there has been a wave of interest in what has been called ductless glandular or hormone therapy. In this field of work, proof seems unusually difficult. One may, however, assume that where there is much smoke there is at least a little fire, and it is incredible that such a voluminous literature should have grown up in relation to glandular therapy unless there were some justification for it. The student of this newer branch of medicine will find much to interest him in its application to the chronic intestinal invalid. The justification for its use in the type of cases under consideration results from the fact that in numerous personal cases one factor after another has been added to the treatment, each additional factor employed resulting in additional gain in the general condition of the patient. Having exhausted every other available factor, and having arrived at a stationary point in progress, it has been possible in many instances to obtain still further progress by the use of glandular therapy. For example, over five years of observation justify the statement that from a clinical point of view results may often be obtained from suprarenal therapy which are not possible without its use. A vast literature exists concerning the suprarenal gland and its possible utilization as an active therapeutic agent. Acute suprarenal deficiencies are becoming more frequently recognized. Sub-acute or chronic suprarenal deficiencies certainly exist in intensity between the acute deficiencies on the one hand and Addison's disease on the other. It is with these intermediate stages of suprarenal deficiency that the physician is concerned in the treatment of the chronic intestinal invalid, and there is little room for doubt that success is more certain with than without the utilization of suprarenal therapy in these invalids suffering, among other things, from chronic exhaustion. For this purpose, a standard grain v whole gland suprarenal preparation has been utilized in the majority of cases showing chronic exhaustion, with or without the accompanying muddy skin previously referred to. Other glandular preparations are frequently employed. Perhaps most often thyroid in amounts from one-tenth to one-fourth grain is useful. In women ovarian preparations are certainly of value in selected cases.

From a strictly pharmacologic point of view the only drug extensively employed is atropin. This is used in a strength of grain $\frac{1}{200}$, repeated from once to four times daily, according to indications. The two indications for which it is employed are to decrease spastic constipation and to decrease general irritability. It has often been found that a small amount of atropin is in itself sufficient to produce the difference between wakefulness and restful sleep, possibly as a result of its nervous sedative action.

In practice, on completion of the history, physical examination and the routine roentgen examination of the gastro-intestinal tract of which fluoroscopic study of an opaque enema is an essential element, the social and mental factors receive first consideration in

the progress of treatment. As soon as these factors are, so to speak, stabilized the diet is taken under serious consideration. In conjunction with diet frequent use is made of mineral oil, agar, yeast and atropin and every attempt is made to take advantage of habit formation and the natural rectal reflexes. As soon as the diet has become satisfactory the application of orthopedic procedures follows, and finally comes the use of the glandular preparations when indicated. Thus by the end of the first four to six weeks all five of these totally independent factors are being simultaneously employed in the effort to bring about, as rapidly as possible, an improvement in the general condition of the patient. Belts are rarely used, since they tend to decrease the faith of the patient in his own ability to carry himself through his day's work. Only slight attention is paid to the question of weight, provided there is not a progressive loss in weight. Not infrequently one may find an apparently healthy person of almost incredible thinness. On the other hand excessive fat is no guarantee of health. Usually, however, the very thin patients will put on at least ten to fifteen pounds in the course of a few months without apparent effort if otherwise satisfactory progress is being made.

Most authorities agree that the treatment of the chronic intestinal invalid is non-surgical in at least 90 per cent. of all cases. Conversely, recovery seems often to vary inversely with the amount of surgery to which the patient has been exposed. It is, however, certain that no patient should be operated upon unless the indications are imperative, for at least six months after intelligent non-surgical treatment has been instituted. During these six months, even if operation is later proved necessary for specific reasons, such as gall-stones or other definite pathology, the patient can have been brought to a status in which operation can be faced with much less probability of a subsequent slump in health.

VI. PROGNOSIS. The application of the procedures above described to a series of 54 chronic intestinal invalids seen in an out-patient clinic, and reported¹¹ two years ago, produced the following results:

No improvement	7 per cent.
Improved	27 "
Improved plus	66 "
Total improved	93 "

This gives a total of better than 90 per cent. of definite improvement, although the condition of 27 per cent. of the cases marked "improved" left something to be desired.

In a consecutive series of fifty private patients, recently reported,¹⁵ the following results were obtained:

No improvement	6 per cent.
Improved	8 "
Improved plus	86 "
Total improved	94 "

Compared with the out-patient cases it will be seen that although the total number of private cases considered as "improved" in all degrees was 94 per cent. as against 93 per cent. in the out-patient series, there is, on the other hand, a distinctly higher proportion of cases marked "improved plus" in the private patient series than in the out-patient series, the figure being 96 per cent. "improved plus" in the private as against 66 per cent. "improved plus" in the out-patient cases, or a difference in favor of the private patients of 20 per cent. considered as "improved plus."

It is therefore justifiable to tell the chronic intestinal invalid that he has a better than 90 per cent. prospect of improvement and that he has a better than 80 per cent. prospect of being very much improved as a result of a few months of non-surgical treatment. This is in itself a helpful point of view for the patient to have. The patient can also be told that he will, if careful, continue to improve for from one to three years after the completion of active treatment.

On the other hand it is misleading to speak of cure. Cure may be apparent but it is always conceivable that a sufficiently difficult combination of circumstances will arise to throw the bodily or mental mechanism out of gear. The trained patient will, however, be able rapidly to readjust himself with a minimum of medical assistance. The best advice to these patients is, after Oliver Wendell Holmes, to the effect that the surest approach to a happy old age is through taking care of an incurable disease.

VII. SUMMARY. 1. Certain impressions and observations resulting from a ten-year study of the chronic intestinal invalid have been presented.

2. Some of the mental and physical characteristics of the chronic intestinal invalid have been outlined.

3. Various contrasts in the practice of acute and chronic medicine, as applied, to the chronic intestinal invalid, have been indicated.

4. The importance of considering all possible factors outside of the gastro-intestinal tract in any attempt at adequate treatment of the chronic intestinal invalid, is referred to.

5. Five distinct and fundamental factors in treatment, all tending to increase the resistance of the patient to fatigue, have been considered.

6. The percentage of improvement obtainable as a result of applying the methods of treatment described, is stated on the basis of two different social groups of patients totalling 104 cases.

VIII. CONCLUSIONS. 1. Patience, persistence and a sympathetic understanding on the part of the physician are prerequisites for successful treatment of the chronic intestinal invalid.

2. The problem being complex and not simple, treatment must be applied from as many different angles as possible in order to produce maximum effect.

3. There are five distinct factors of fundamental importance in treatment. These are:

1. Social.
2. Mental.
3. Dietary.
4. Orthopedic.
5. Glandular.

The common objective of all these factors is increased resistance of the patient to fatigue.

4. These five fundamental factors in treatment must be applied in overlapping sequence in order to yield the maximum benefit.

5. The chronic intestinal invalid usually recovers at a rate inversely proportionate to the amount of surgery to which he has been exposed.

6. The physician who will take the time and trouble may promise the chronic intestinal invalid a 90 per cent. prospect of a reasonable degree of improvement, and an 80 per cent. prospect of a marked or satisfactory degree of improvement as a result of a few months of non-surgical treatment according to the methods above outlined.

7. Treatment which does not train the patient to avoid or to recover from future relapses with a minimum of medical assistance, falls short of what the chronic intestinal invalid has a right to expect from his physician.

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ON THE ETIOLOGY OF TYPHUS FEVER.*

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For more than fifty years scientists have sought for the etiologic agent in typhus fever and still the cause remains undiscovered. During the past thirty years there have been more than twenty organisms held forth by various workers as the cause, or probable cause, of typhus fever. It is not my purpose to review the enormous literature which has accumulated from the earlier studies, interesting as that might prove to be; however, in view of the fact that the Great War somewhat interfered with the American profession keeping abreast with the contributions made along these lines in Europe, especially in Germany, it seems worth while to present the more important contributions which grew out of the serious typhus situation in Eastern Europe and, what seems to be, the real status of our knowledge at the present time regarding the causative agent of this disease.

To some the discovery made by Plotz²⁴ in 1914, and subsequently enlarged by him and his associates,^{1 23 25 26 27} seemed to be the final solution of this difficult problem. Indeed, there are authors of text-books in bacteriology who have practically accepted this organism as the cause of typhus fever. True, the organism seemed to have more in its favor than did even the most promising of those previously upheld as the cause of typhus fever, but it cannot be said that sufficient evidence has been adduced to justify its being named "*B. typhi-exanthematici*."

The organism which Plotz described is a small pleomorphic, Gram-positive bacillus, which is non-motile, not encapsulated and not acid-fast. It is an obligate anaërobe and requires a rather select culture medium. Its length is said to vary from 0.9 to 1.93 microns, its breadth from one-fifth to three-fifths its length. The organisms are straight; occasional ones are slightly curved. The ends are rounded or slightly pointed. Coccoid forms are said to occur. With special stains an occasional organism shows a small polar body at one end; more rarely at both ends. The colonies usually appear in the culture tubes in about ten days; occasionally as early as the fifth day or as late as the nineteenth day. They appear first as opaque spots, which by direct light appear white. Subsequently they assume a "Y"-shaped growth, surrounded with a zone of brownish precipitate. The organism has been isolated from both Brill's disease, the mild American form of typhus fever, and epidemic

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typhus fever. It has been grown from typhus infected animals and from infected lice. The organism shortly after isolation is slightly pathogenic for guinea-pigs; it loses its pathogenicity very rapidly. In the human host it induces the formation of specific agglutinins, precipitins, opsonins and complement-fixing antibodies. These are, however, detectable chiefly during the convalescent period. The agglutination readings average in the neighborhood of 1 to 200; only in one instance recorded going as high as 1 to 1600. These shall be discussed more fully further on.

In spite of the elaborate studies made by Plotz and his associates, their results cannot be said to show more than the fact that the organism is found in typhus fever patients. This much we must acknowledge in face of the cultural results and the serologic studies. But simply because an organism is found in a given disease does not license one to claim for it an etiologic role in the disease. The fact that it possesses a degree of pathogenicity for animals susceptible to the disease in question is of little significance unless the typical disease picture is reproduced. This includes not only the typical course of the disease but also the reaction induced by the disease, in other words, immunity relationships, if any occur. It is a well-known fact that typhus fever leaves an absolute immunity to further attacks in both man and animals. This immunity can be easily proved in animals by reinoculating them with the blood of a typhus fever patient subsequent to the animal's recovery from the disease, and in studying an organism isolated in typhus fever this procedure should be carried out extensively to determine whether or not it, in addition to producing the characteristic disease in a typhus susceptible animal (preferably a guinea-pig), also conveys definite immunity against subsequent inoculation with virulent typhus blood. Plotz and his associates did not succeed in reproducing even the disease picture in animals. The reason for this is laid to the extremely rapid loss of virulence of their organism on artificial media. But the fact remains that neither the disease picture nor what is more important, immunity reaction, was produced by inoculating their organisms into experimental animals. Their claim that the organism is the cause of the disease then rests solely upon cultural and serologic grounds and is unsupported by conclusive immunologic results.

In the autumn of 1915, Weil and Felix⁴⁶ isolated from the urine of typhus fever patients two strains of *Proteus vulgaris* which they named X1 and X2. These they found were markedly agglutinated by the sera from typhus fever patients, and on making control examinations learned that they were not dealing with ordinary saprophytes. The application of this discovery to the laboratory diagnosis of typhus fever was soon recognized by them. In the spring of 1916 they isolated another strain of this bacillus, also from the urine of a typhus fever patient, which they named X19.

This strain differed from the other two in that sera from typhus fever patients agglutinated the organism in dilutions many times higher than either of the other two—at that time one instance as high as 1 to 50,000. This organism has therefore, superseded the other two in the new serodiagnosis of typhus fever. It is not within the scope of this paper to discuss the technic of this method. In general it is not unlike the Gruber-Widal reaction. The reliability and diagnostic facility of this reaction has been confirmed by many workers and it has found a place in the diagnosis of typhus fever throughout Europe. It is diagnostic in practically 100 per cent. of the cases. The organism (*Proteus* X19) can be grown easily on ordinary nutrient media and may be kept for months without transplanting. In 1916 Dienes,^{3,4} succeeded in isolating these X-strains from the blood of the typhus fever patients in 30 per cent. of cases which he examined. The reason why *Proteus* X19 has not been isolated in a higher percentage of cases was found by Felix⁷ in 1917 to be due to the sensitiveness of the X-strain to the acid production of other bacteria in the urine and stools; to its sensitiveness to changes in media and, in the blood stream, to the rapid setting in of the bactericidal substances. Friedberger,⁸ in 1917, on the basis of pathogenicity for guinea-pigs, agglutinins, precipitins, complement-fixation and Pfeiffer's phenomenon, maintained that *Proteus* X19 was probably the etiological agent in typhus fever. But in 1918 Landsteiner and Hausmann,¹⁴ as well as Doerr and Pick,⁵ and in 1919 Mollers and Wolff,¹⁶ proved that *Proteus* X19 would not immunize guinea-pigs against typhus fever; that is, animals inoculated with blood from typhus fever patients subsequent to their recovery from *Proteus* X19 infection, developed typhus fever. We have here then an organism which, though occurring with remarkable regularity in typhus fever, apparently bears no etiologic relationship to the disease. This is especially interesting in view of the very pronounced serologic responses which the organism induces and the promptness with which the antibodies put in their appearance, generally within the first week of illness.

Now, let us compare the serologic responses induced by the Plotz bacillus with those produced by *Proteus* X19. It was previously stated that Plotz and his associates were unable to supply proof on immunologic grounds that their organism really was the cause of typhus fever and that the arguments for naming the organism "*B. typhi-exanthematici*" rest chiefly on a cultural and serologic foundation. The inadequacy of these arguments become obvious in a comparison of the agglutination readings of the two organisms in question. The average readings with the Plotz organism are figured from the readings given in one of Plotz's publications²⁵ and the average readings with *Proteus* X19 are obtained from one hundred readings made by Professor Oettinger²² in studying the Weil-Felix reaction and the biology of *Proteus* X19. My figures show that

during the febrile period the Plotz organism is agglutinated by the patient's sera in dilutions of 1 to 8, at the time of crisis 1 to 113 and fifteen days after the crisis 1 to 220. The readings during the febrile period were for the most part negatives (readings below 1 to 50 were counted negatives), the highest reading being only 1 to 100. At the time of crisis they ran about half negatives, the highest reading being 1 to 800, and after the crisis they ran from negatives to 1 to 1400. Let us compare with these figures the averages of one hundred readings made by Oettinger in his studies on the Weil-Felix reaction. It will be observed that the agglutinins for X19 are far more concentrated and appear earlier in the disease. On the average eighth day of illness the agglutination readings average 1 to 2424, varying from 1 to 25 to 1 to 60,000 during the febrile period. On the average tenth day after the crisis the readings average 1 to 2540, one instance as high as 1 to 25,000 on the eleventh day. My own observation with the Weil-Felix reaction made while I was serving as bacteriologist for the American Red Cross Commission to Germany, satisfy me that the readings run a very high average, and in occasional cases exceptionally high. Indeed, a few of the workers have placed 1 to 200 as the lowest positive reading, which is practically as high as the average readings obtained with the Plotz organism at the time of crisis. It should be noted that the Plotz organisms show a degree of spontaneous agglutination which should also be allowed for in making this comparison. In short, we see that the agglutination readings obtained in using the Plotz bacillus are *nil* compared with those obtained in using *Proteus* X19, an organism which for these very reasons Freidberger felt justified in championing as the cause of the disease. Without proof on immunologic grounds and with serologic values which are negligible, what argument is there really left for upholding the Plotz bacillus as the cause of the disease?

Significance has also been attached to vague results supposed to have been obtained by attempted prophylactic immunization of people against typhus fever with the Plotz organism. In the winter of 1915-1916, Plotz, Olitsky and Baehr²⁶ inoculated 8420 persons, members of hospital, sanitation and other units in Serbia, Bulgaria and Volhynia, with a vaccine prepared from their organism. Out of this number six developed typhus fever during the four months of the epidemic. In other words the immunity, if any was really conveyed, was, at any rate, not absolute or complete. It therefore does not yield an added argument in favor of the organism being the cause of the disease. They were unable to obtain statistics as to the prevalence of the disease in the regions where they vaccinated so that one is at loss to even speculate on what possible decrease in the incidence of the disease might have resulted from these vaccinations. But it would seem that six cases among 8420 persons in a period of four months is not a negligible incidence of the disease.

Another important factor with which we are unfamiliar is the degree to which the various organizations enforced other prophylactic measures and the employment of typhus immune persons for the more hazardous duties in the handling and care of typhus fever patients, such as those of cleaning up the patients in the admitting office, etc. In short the results of the above experiments do not seem to furnish any added argument in favor of the Plotz organism being the etiologic agent.

But the question may be asked: Is not the fact that the Plotz organism has been grown from infected lice an excellent argument in favor of its being the causal agent of typhus fever? To this the reply would seem to be a question: Whence comes *Proteus* X19? It seems to me not improbable that the human infection is derived from the louse, and it is not unlikely that a number of other secondary organisms are introduced by the louse. The diplobacillus of Rabinowitsch,³⁰ also markedly agglutinated by the patient's sera, is probably another member of such a group. In brief, there are excellent reasons for believing that in typhus fever we have as a regular thing a state of mixed infection and that the organisms associated with the active virus of the disease are most probably introduced by the louse. There may be a state of symbiosis. It is worthy of note, in this connection, that Widmann,⁴⁹ in 1915 cultured a small Gram-negative, anaërobic, bacillus from normal lice. It is possible that quite an array of bacteria might be cultivated from both normal and infected lice.

This brings us to one of the most fascinating chapters in the history of research on the etiology of typhus fever, namely, that dealing with the development of our knowledge of the so-called *Rickettsia*. These studies were begun by Ricketts and Wilder³² about ten years ago, but not until recently was there an appreciable advance made in our knowledge concerning them. Ricketts and Wilder,³² in 1910, while working on the etiology of typhus fever in Mexico, made a large number of smear preparations from the digestive tracts of infected lice which they stained by the Giemsa method. They found that these smears contained large numbers of characteristic bipolar staining organisms. The thing that disturbed the significance of their observations at the time was the occasional occurrence of the same sort of organisms in smears which they prepared from normal lice. The fact that they dealt with two closely related organisms, one found exclusively in infected lice, has come to our notice through more recent investigations to be discussed presently. The observations of Ricketts and Wilder were confirmed by Prowazek²⁸ in 1913; by Sergeant, Foley and Vialatte³⁹ in 1914, and by others.

In 1915 da Rocha-Lima^{33 34 35} prompted by the earlier observations made on smear preparations of infected and normal lice, determined to study the lice by histologic methods, hoping that

this might clear up the confusion regarding these bodies. This proved to be a fruitful idea. It revealed the fact that a state of intracellular parasitism existed in typhus infected lice, involving the epithelial cells of particularly the gastrium. The control examinations showed that such a condition never occurred in non-infected lice—lice obtained from a typhus-free region. The involved cells of the gastric mucosa are found to undergo striking alterations so that their identification is frequently possible under the low power of a microscope. Within the cells the parasites, when few in numbers, are found to lie together in a group sharply rounded off from the rest of the cytoplasm. This is the picture early after an invasion, but as time goes on and the parasite multiplies the cells become entirely filled with the parasitic bodies and eventually cause them to be ballooned-out into the lumen of the stomach, protruding from the mucosa like droplets of fluid. Miss Sikora⁴⁰ observed the same involvement in the cells of the salivary glands. The parasite itself, da Rocha-Lima informs us, impresses one as a very small bacterium—smaller than *M. melitensis* or *M. prodigiosus*, but under very high magnification it appears not round but ellipsoid or olive-formed. These ellipsoid bodies lie for the most part in pairs, end to end, connected by a less intensely stained intermediate and surrounding substance. These double forms have the appearance of dumb-bells. Single forms also occur; the products of a recent division, but these are in the minority. Da Rocha-Lima estimates the single as 0.3×0.4 of a micron in size and the double or mature forms as 0.3×0.9 of a micron. Their staining qualities are of special interest. They stain very feebly or not at all with the ordinary bacterial stains, such as carbol-fuchsin, carbol-thionin, methylene blue, etc. They stain best and most characteristically with Giemsa, taking this stain differently than do bacteria. With this method they stain a pale ruby-red, almost the same coloration as nuclei take with this stain; however, not so bright a red, but more like the coloration which one obtains by this method on spirochetes and the tails of spermatozoa. Bacteria with this method generally stain a dark-red or an outspoken blue. The organism cannot be stained by Gram's method. Though many special methods were employed, all endeavors to cultivate the organism have failed. Da Rocha-Lima also noted the occasional occurrence of similar bodies in normal lice, but observed that these, without exception, lie extracellularly in the lumen of the digestive tract. These, undoubtedly, were the source of confusion in Ricketts' time when lice were studied entirely by smear preparations. Those of interest in connection with typhus fever are the intracellular forms found exclusively in typhus infected lice. For these da Rocha-Lima proposed the name, "*Rickettsia-Prowazeki*," in honor of these two scientists who gave their lives in studying the etiology of typhus fever. Other—what seem to be—species of this new group of

organisms have since been described, and to these I shall refer at the close of this review on the Rickettsia.

Let us now take up the evolution of this phenomenon of intracellular parasitism in infected lice. Da Rocha-Lima showed experimentally that the louse is incapable of transmitting the virus of typhus fever until at least five days after the louse has fed on a typhus fever patient. In other words a definite period for development or evolution is required by the organism in the intermediate host. Now, what light does da Rocha-Lima's histologic studies throw upon this phenomenon? Namely this, that the cells do not show an involvement previous to the fourth day after the louse has been infected, while after that period of time the phenomenon is present with regularity. His method of studying the development of the virus in lice is deserving of mention. The experimental lice were kept in a cleverly designed cage of very finely meshed screening (several of these which were left by him in Warsaw, Poland, at the time the Germans were driven from that place, were later utilized in our own studies). The cages containing the lice were tied to a patient twice a day for one hour and the rest of the time were kept in a thermostat at 33° C. He found that lice kept at a temperature of 23° C. between the usual feedings did not develop the Rickettsia and, furthermore, that injections of emulsions of the viscera of such lice into guinea-pigs did not result in an infection. Da Rocha-Lima showed also that the infection of the female louse may be inherited by its offspring.

Da Rocha-Lima³³ was the first to successfully infect guinea-pigs with typhus fever by direct inoculation of the virus in the form of emulsions prepared from the organs of virulent lice. The animals thus inoculated, after having undergone the usual course of the disease, were found to be immune to subsequent inoculation with blood taken from typhus fever patients. He found that the infectivity of such emulsions from lice was in direct proportion to the numerical content of Rickettsia. In one instance da Rocha-Lima succeeded in carrying on the louse virus, in passage from guinea-pig to guinea-pig, for nearly one year, during this time passing it through twenty-three animals. Blood from the eleventh passage was injected into a monkey, *Macacus sinicus*, which developed the typical disease after an incubation period of eight days.

More interesting still are da Rocha-Lima's³³ studies on prophylactic immunization, using guinea-pigs as his subjects and a vaccine prepared from virulent lice. The lice used for the preparation of the vaccine were fed on typhus fever patients and kept under conditions which would ensure the greatest development of the Rickettsia. Emulsions were then prepared from the viscera of these lice and the virus was attenuated by aging it for a number of weeks. The vaccine so prepared was administered hypodermically. The best results, absolute immunity of the entire series of animals, were

obtained by making three inoculations within the space of one week with a vaccine allowed to age for three weeks; the first dose containing an emulsion of five lice, the second ten and the third twenty lice. The experiments were controlled with normal guinea-pigs; the entire group, vaccinated and controls, received the usual infecting dose of blood from typhus fever patients. The non-vaccinated pigs contracted the disease, while the vaccinated ones, with a negligible exception, failed to show any reaction whatever.

It has been stated that other—what seem to be—species of *Rickettsia* occur in Nature. Before taking these up, let us review the features which separate the *Rickettsia prowazeki* from the rest, biologically, if not otherwise: (1) The *Rickettsia prowazeki* have a specific intermediate host, namely, *Pediculus vestimenti*. That the human louse is essential for the development of the *Rickettsia prowazeki* was demonstrated by the researches of Nöller.¹⁹ He fed pig lice and human lice on typhus fever patients at the same time. The *Rickettsia* developed in the human but not in the pig lice. There is one slight exception to this specificity, for Toepfer^{42 43} and Toepfer and Schussler⁴⁴ whose studies confirmed for the most part da Rocha-Lima's work, claim to have observed the development of the *Rickettsia prowazeki* also in the human head louse, *P. capitis*. The biologic difference between *P. vestimenti* and *P. capitis* must be so small, if any, that the development of the *Rickettsia prowazeki* in the head louse need not be looked upon as a deviation from the specificity of the intermediate host. (2) The *Rickettsia prowazeki* are intracellular parasites of the louse.

Now let us turn briefly to the organism which was the source of confusion to Ricketts and Wilder and others since then, namely, the one occasionally found in normal lice. Nicolle, Blanc and Conseil,¹⁷ working in Tunis in 1914, found that 5 per cent. of lice examined (smear preparations) in a typhus free region contained *Rickettsia*-like bodies. Brumpt,² in 1918, found them in smear preparations in 73 per cent. of lice taken from seven healthy war prisoners. This matter was also studied by da Rocha-Lima histologically. He found that whenever these bodies were found to occur in normal lice they were distributed over the surface of the gastric mucosa and never were found to lie within the cells even though they are found to lie in a rather thick layer against the mucosa. He further observed that though this organism was very similar to the *Rickettsia prowazeki* it was thicker and plumper and stained with greater ease than the *Rickettsia prowazeki*, though still not so easily as did the ordinary bacteria. Da Rocha-Lima named these *Rickettsia*-like organisms in normal lice, *Rickettsia pediculi*.

The same kind of organisms have also been found to occur in lice taken off patients suffering from Wolhynian fever, a disease similar to or synonymous with trench fever. These have been studied

particularly by Toepfer,⁴¹ Jungmann^{10 12} and by da Rocha-Lima.¹⁵ They have been observed in as high as 80 per cent. of lice removed from patients at delousing stations, and are found to also occur in the form of a layer upon the gastric mucosa, though here one occasionally does observe a slight degree of intracellular invasion. Jungmann has named this organism, *Rickettsia wolhynica*.

None of the three above-named *Rickettsia* have yielded to artificial cultivation. This might cast a possible doubt on their actually being organisms, were it not for the fact that one species of this new group of organisms has recently been cultivated. The discovery was quite accidental. Nöller,^{20 21} in 1917, while cultivating the *Crithidia melophagi*, a flagellate occurring in the sheep louse, *Melphagus ovinus*, found growing together with the *Crithidia* in separate colonies, a microorganism which in every respect looked like the *Rickettsia*. He named the organism *Rickettsia melophagi*. The following year Jungmann¹¹ confirmed and elaborated the studies of Nöller. The organism grows easily on the surface of a "sheep-serum-grape-sugar-agar" at 28° C. The colonies appear in six to eight days as minute, punctiform, translucent, round colonies, which on microscopic examination prove to be pure cultures of *Rickettsia*. Jungmann also studied the sheep lice histologically and found these bodies overlying the gastric mucosa, rarely noting even a slight intracellular involvement. He found that the infection was a constant one and, in a cleverly conducted research, established the fact that the lice obtained the infection by hereditary transmission and not from the blood of the sheep upon which they fed. The organism possesses absolutely no pathogenicity for any animals.

From the review of these researches on the *Rickettsia* we gather that an entirely new group of organisms has been discovered, a group seemingly occupying a position closer to protozoa than to bacteria.

It is thought by some that the *Rickettsia prowazeki* and the Plotz organism probably are one and the same organism. It is rather difficult to see wherein the likeness lies, and if the original description given by Plotz had not been later qualified in a remarkable way, there would, of course, have been no dispute as to their dissimilarity. Shortly after da Rocha-Lima's first publication on the *Rickettsia* appeared, Olitsky, Denzer and Husk²³ published the results of their studies in Mexico, in which they reported that they had grown the Plotz organism from infected lice. In this paper we get, for the first time, the remarkable fact that the Plotz organism is not always Gram-positive. They state: "In some of our blood cultures, however, smears made directly from colonies showed only bacilli which were completely decolorized by Gram's method. In other cultures the predominating organisms were Gram-positive, with numerous Gram-negative bacilli scattered throughout the

field. In subsequent subcultures the bacilli always became Gram-positive." Then they refer to the publication by da Rocha-Lima³³ as confirming their results. They state, referring to their cultures from lice, "In recent studies by da Rocha-Lima, further corroboration of this fact is made; he finds that infective lice harbor an organism of similar morphology in enormous numbers, especially in the stomach walls, and, remarkable to state, these organisms are Gram-negative." Strange to state, da Rocha-Lima does not acknowledge any such similarity. In the first place the *Rickettsia* are, strictly speaking, neither Gram-positive nor Gram-negative; they simply will not stain by Gram's method, because, for one thing, they do not stain readily with the simple bacterial stains. Outside of the unusual phenomenon with reference to the Gram-stain, Plotz does not mention any special staining qualities for his organism, and it is to be implied that it has the qualities of ordinary bacteria in respect to the simple stains. Besides, there is little in common morphologically between the two organisms. All attempts to grow the *Rickettsia prowazeki* seem to have failed in spite of the suggestions which might have grown out of the methods employed by Plotz and his associates. Finally, the one species of *Rickettsia*, *Rickettsia melophagi*, which has been cultivated, proved to be an aërobe, and it is not improbable, therefore, that the *Rickettsia prowazeki* is also an aërobe, rather than an anaërobe, as is the Plotz bacillus. The staining qualities, the sort of development in the louse, and the hereditary transmission of infection in lice resemble the activities of protozoa more closely than those of bacteria.

So much for the *Rickettsia* as observed in typhus infected lice. Though the grounds are less secure, it is, nevertheless, interesting to note the instances where *Rickettsia*-like organisms have been observed in the blood and tissues of typhus fever patients and experimental animals. Ricketts and Wilder³² observed them in Giemsa-stained blood smears of typhus fever patients and in fresh preparations. They described the organism as a short bacillus which at first sight appeared solidly stained, but on minute examination showed an unstained or faintly stained zone across the middle. The fresh preparations also showed a differentiation of the forms into two halves, separated by a line or narrow zone of substance of a different refractive character, the organism possessing, not motility, but more or less rapid vibration. In 1911 Nicolle observed such bodies in the neutrophilic leukocytes of typhus infected chimpanzees, and Consiel and Conor¹⁸ and Givino and Girard⁹ in the same year in the neutrophilic leukocytes of typhus fever patients (Reder³¹). In 1913 Prowazek²⁸ made the same observations. He states that they occurred as oval and diplo-forms, lying in vacuoles, generally at the periphery of the leukocytes, and, with the Giemsa stain, colored a carmine-red, and were distinguishable from the neutrophilic granulations of the leukocyte. Da Rocha-Lima³⁶ has also observed

in blood smears from typhus fever patients as well as in histologic sections and smears made from tissues of typhus cadavers, structures which, in size, form and coloration, appeared the same as the *Rickettsia*. He tried out a large number of different staining methods, but was only able to demonstrate them when using the Romanowsky-Giemsa method.

In close association with the observation just described are those of Dr. Ludwig Anigstein, of the Central Epidemiologic Institute, at Warsaw, Poland, and myself, working together under the American Red Cross Commission to Poland. It was planned, as a part of our work, to carry on extensive studies on the distribution of these *Rickettsia*-like organisms in the tissues of typhus guinea-pigs and monkeys, and, as far as possible, human cadavers. But this part of the work did not materialize for reasons beyond our control. We were forced to limit our studies to blood smears and fresh blood from typhus fever patients. Doctor Anigstein prepared something like one hundred and fifty blood smears, representing about fifty distinct samples of blood from different periods of the disease. These he stained by various methods, chiefly with Giemsa and Leischmann stains. While these preparations were very interesting from the standpoint of striking nuclear changes, which will be written about later, only rarely were there bodies observed in the leukocytes which answered to Prowazek's description. One frequently sees, what seem to be exceptional inclusions of minute bodies, but to determine their morphology with accuracy is generally out of the question. However, bodies corresponding to the *Rickettsia* in shape, size and coloration were occasionally found lying free in the blood plasma.

To us the most interesting observations were those that we made with a dark-field; using a special Zeiss lens giving a magnification of at least 2000 \times . We examined by this method over fifty specimens of blood obtained from nearly as many different typhus fever patients in different stages of the febrile period of the disease. Of these 90 per cent. showed dancing bodies which in morphology, refractility and size were the same as those we observed in dark-field preparations of infected lice, which were made for comparison and afterward stained to further establish the presence of *Rickettsia*. These bodies occurred as single or ellipsoid forms but chiefly as the double or dumb-bell forms. It is extremely difficult to identify the single forms but the double forms are quite characteristic. The double forms really have the appearance of dumb-bells, two oval bodies being held together in their long axes by a less refractile fluid-like substance lying intermediately and frequently seen to surround the oval bodies. They are readily distinguished from the microsomes, or so-called blood-dust, in that these are much more refractile, generally larger and differ somewhat in morphology. As to numbers it was found that on

examining a capillary film between the slide and cover-slip under the magnification described, their number varied anything from one to five per field. No studies to determine their relative incidence in various periods of the disease were undertaken. The specimens were obtained by vena- and finger-puncture and special care was taken in the preparation of the glassware used. For financial reasons the work of the American Red Cross had to be materially curtailed and our work came to a premature close so that more extensive studies were out of the question. Twenty-five specimens of normal blood examined by the same method and with equal care failed to show these Rickettsia-like bodies.

I should like to now present certain arguments in favor of the etiologic agent of typhus fever being a protozoön or an organism related to the protozoa rather than a bacterium. In the first place the studies by da Rocha-Lima and others show that the louse as an intermediate host is not very unlike the anopheles mosquito in the spread of malaria. The louse does not serve as an intermediate host in the same way that the flea does in transmitting the Pest bacillus, by carrying the organism in its digestive tract. The phenomenon of intracellular parasitism in typhus infected lice, involving even the cells of the salivary glands, preceded by a definite period of development during which time the louse is non-infective, are features that one immediately associates with protozoan organisms. To this may be added the actual necessity of an intermediate host in the spread of the disease and the specificity of the intermediate host. The possibility of hereditary infection among lice must also be considered. Clinically, the exanthema and the characteristically limited course of the disease seem to point to a protozoan cause. Likewise suggestive is the characteristic onset with chills. Finally the Wassermann reaction in typhus fever points to a protozoan-like cause of the disease. Jablons,¹³ in 1914, showed that during the florid period of the disease typhus fever may give positive Wassermann complement-deviation in practically 90 per cent. of the cases.

Conclusions. 1. There is no conclusive evidence that the *Bacillus typhi-exanthematici* of Plotz is the cause of typhus fever.

2. *Proteus* X19 has more in favor of its being the cause of typhus fever than the Plotz bacillus, but on immunologic and other grounds it appears that both of these bacteria are secondary invaders.

3. There is evidently a state of more or less mixed infection in typhus fever.

4. There may be a state of symbiosis.

5. The *Rickettsia prowazeki* are probably the cause of typhus fever.

6. The *Rickettsia* seem to constitute a new group of micro-organisms, probably more closely related to the protozoa than to the bacteria.

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ACUTE EPIDEMIC ENCEPHALITIS.

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AND

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Introduction.—Many comprehensive papers have been published upon the subject of acute epidemic encephalitis by such writers as Economo, Wilson, Bassoe, Tilney, Neal, Barker, Flexner, House and others, so that it is not necessary to do more in this paper than to give a brief symptomologic analysis of our 20 cases which we have had the opportunity to study.

Our first case was seen in February, 1919, the others during 1920, seen in private practice, in the wards of the city hospital, in consultation and as representative of the State Department of Health.

The clinical phenomena or symptoms of this disease are caused by an acute infiltrative inflammation of the central nervous system, especially about the optic thalamus, the floor of the fourth ventricle and in the white matter of the brain and cord.

Classification.—Several writers have classified their cases into different groups according to the predominant clinical picture or to the portion of the nervous system involved. MacNulty, Tilney and Sabatini have made these classifications, which are helpful in calling attention to its resemblance to other diseases, but after a study of our 20 cases we have found that if the disease is seen in its early stages and observed during its entire course in nearly every case all the typical symptoms can be demonstrated.

Prodromata.—As Flexner has pointed out the prodromal symptoms have not been clearly defined. This has been due to the fact that most of the cases reported have not been observed until late in the disease. We have been able to study 18 of the 20 cases during the first week of their illness.

The disease usually begins with symptoms that resemble and have frequently been mistaken for influenza. They were catarrhal manifestations of the mucous membranes, of the upper respiratory tract with malaise, headache, general pains, mild or very severe, and frequently nausea, vomiting and constipation.

In some cases (as in Cases 1, 3, 5 and 15) these prodromal symptoms precede the typical symptoms by more than a week, while in others (as in cases 2, 4, 7, 11, 12 and 20) the prodromal period lasted only three days.

We were unable to determine the period of incubation, as no 2 cases occurred in the same family and there was no history obtainable of contact with a previous case outside the family. In 2 cases

the onset was sudden, in one (Case 6) with marked restlessness and delirium and in another (Case 19) with pronounced lethargy.



FIG. 1.—Case III. Sixth week of disease. Patient markedly improved, still shows partial bilateral ptosis, of eyelids and mask-like face.



FIG. 2.—Case IV. Patient improving; sixth week of disease still showing mask-like expression, ptosis and partial wrist drop.

Headache in varying intensity was present in all our cases.

Vomiting was only recorded in 8 cases and never was severe or continuous.

Constipation occurred in 14 cases, and this was also moderate in degree.

Other prodromal symptoms were severe muscular pains in the neck, shoulders and extremities in 12 cases, tonsillitis in 3 cases and nose-bleed in 1 case.



FIG. 3.—Case XVI. Patient shows ptosis of lids; mask-like face; lethargy marked; taken second week of disease.

The Disease.—The average duration of the fever was seven days. It was frequently present at the onset, but in some cases not until



FIG. 4.—Case XVI. Same taken third week of disease; shows profound lethargy; mask; ptosis; and dropping of lower jaw.

later in the disease. In mild cases it varied between 99° and 101° or 102° , but in fulminating cases, or those with complications, it

read as high as 107° . The age of patients varied from nine to seventy-eight years. There were twelve males and eight females.

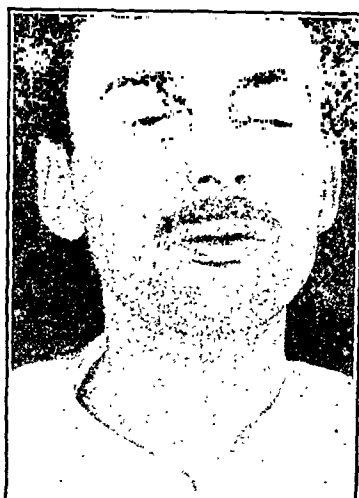


FIG. 5.—Case II. Fourth week of disease, showing bilateral ptosis; mask expression and left external squint.

Cranial Nerve Involvement.—Double vision was present in seventeen cases. We concur with William House that this symptom only

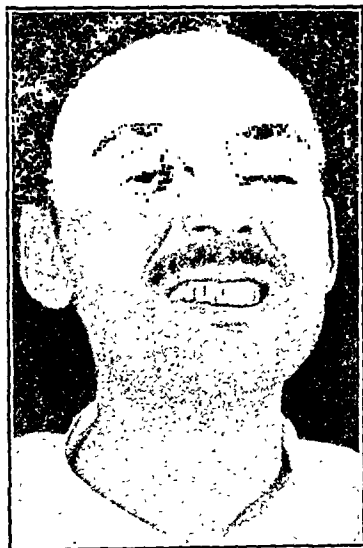


FIG. 6.—Case II. Fourth week, showing marked paralysis of both lids, particularly the left, and partial right facial paralysis.

lasts from two to four days in most cases, and was usually associated with some blurring of vision.

It was the first typical symptom of the disease to appear in 6 cases (Cases 2, 3, 4, 7, 12 and 13).



FIG. 7.—Case II. Second week of disease, showing marked catatonia of arms and partial wrist-drop.

This was clearly brought out in Case 2. A factory girl who used a large lever in her work, suddenly noticed that there were two levers instead of one and immediately reached out for the wrong one. She complained of this to the foreman of the factory.

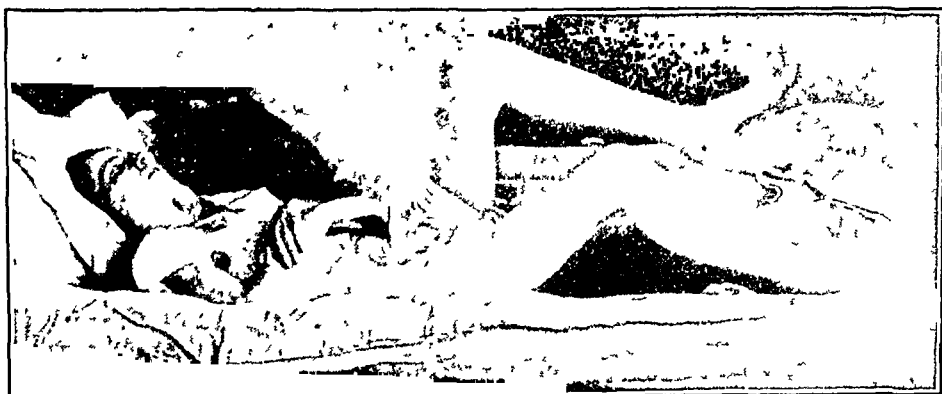


FIG. 8.—Case II. Second week, showing catatonia of legs and general character of patient.

Third Nerve. This paralysis occurred in 18 cases. Bilateral ptosis was the most constant and striking cranial nerve symptom. It varied from a slight weakness to a marked paresis lasting throughout the course of the disease. The first definite improvement was often heralded by the raising of the eyelids voluntarily.

Fifth nerve paralysis was present in 9 cases. It was chiefly a

masseter muscle paralysis giving the symptoms of dropping of the lower jaw and difficulty in chewing.

Sixth Nerve. Six cases had an internal squint which was usually unilateral.

Seventh Nerve. Next in frequency to the third nerve involvement was that of the seventh nerve. The paralysis was either very slight or in some cases very pronounced. This was usually unilateral, involving particularly the right side, and when a bilateral paralysis occurred it was more marked on the right side.

The eighth nerve as far as we could tell by ordinary methods was not involved in any case.



FIG. 9.—Case II. Taken second week of the disease. Patient in deep lethargy. Note mask-like expression, marked ptosis of lids and dropping of lower jaw, due to weakness of masseter muscle.

The ninth nerve was affected, producing dysphagia in 7 cases.

Tachycardia was in evidence in 5 cases. Some claim this to be due to a tenth nerve involvement.

The eleventh nerve was affected in 3 cases involving the trapezius and sternocleidomastoid muscles.

A tremor of the tongue and slurring speech, such as that seen in general paresis, was observed in many cases, but no definite number can be given, however, as we failed to record this symptom in every case. This by some authors is conceded to be a twelfth nerve involvement.

The most striking general symptom seen in our series of cases was a disturbance of consciousness, progressive in character, varying from apathy to coma. It usually developed by the end of the first week. In a few cases it occurred earlier and in others later in the course of the disease.

SYMPTOMATIC CHART OF CLINICAL SYMPTOMS:

[illegible]

Fig. 10.—Chart of frequency of symptoms in this series. Arranged in percentage order.

This lethargy is not as profound as one would expect from the appearance of the patient, as they were easily aroused when spoken to and answered questions intelligently in the early stage. As the lethargy increased it became much more difficult to elicit responses. Some cases, while apparently lethargic, were really restless and excited with muttering delirium. It was only during the early stage of lethargy that we noted catatonia as a symptom. The lethargic state lasted from two weeks to three months in our series, disappearing gradually.

Delirium was a symptom in 17 cases. It occurs usually early in the disease and of a mild type. In 2 cases it was maniacal in nature. The patients seem to realize their actions in mild cases. In a few restraint was required. Insomnia was present in 16 cases. Many cases required hypnotics.

Restlessness was evident in 13 cases. This restlessness existed in all forms, from a sense of general discomfort with inability to assume a comfortable position, to a marked tossing about or attempts to get out of bed.

Catatonia was an interesting and unusual symptom to be seen in an acute epidemic disease and was present in 16 cases. It has a distinct place in the course of the disease and occurs early during the period of lethargy. In no one case did it appear before the onset of lethargy, and as the lethargy tended to be prolonged the catatonia began to disappear. It could be elicited best by raising the arms or legs. They would remain in this position for some time and then tend to drop slowly to their normal position.

Ataxia was noted in 18 cases and occurred usually at the onset of the disease. It was most pronounced in the arms and was of an intentional type, noticed more particularly when the patient was asked to pull down his sleeve or reach out for some object. The ataxia of the legs was evident in many cases and resembled in some cases the cerebellar type, causing the patient to circle to the left or right.

Choreiform movements were in evidence in 11 cases. They resembled all the types seen in chorea from the mildest to the most severe, but particularly affecting the right side. Other writers have reported on this condition but not in nearly as large a percentage of cases. When the symptom is pronounced it must be differentiated from true chorea.

Muscular fibrillation, a marked twitching of various muscles or muscle groups, existed in all cases charted, or 100 per cent. It was a very interesting and suggestive symptom, and in fact so distinctive and characteristic as to make one immediately suspect encephalitis when it is seen. Most of these cases presented twitching (particularly of the lips, nasal muscles). Some had twitching of the arms and legs and a few of the intercostal and abdominal muscles. The rate of twitching was about 75 per minute, and in our opinion is a

most convincing symptom. It may be general or local or it may occur in all parts of the body at different intervals.

Parkinson's mask occurred in all but one case, and when once seen it cannot be forgotten, as it certainly resembles the mask seen in paralysis agitans and together with the muscular tremor has led many writers to describe a paralysis agitans group.

The tremor noted in 100 per cent. of the cases was coarse in type and increased by purpose—in other words, an intention tremor. This disappeared during actual sleep and returned upon awakening the patient.

Eruption was present in 3 cases, in 2 it was herpetic upon the face and legs and in 1 it was a marked purpura of both arms, legs and shoulders. This patient finally developed gangrene of the toes. The gangrenous area was on all toes and extended to the ankle.

Among the other paralyses seen in our series were 5 cases presenting paralysis of the arms and legs. It was noted that these all began on the right side. These cases resembled anterior poliomyelitis, but were associated with a severe polyneuritis. As the neuritis improved so did the paralysis.

Partial wrist-drop and foot-drop occurred in 4 cases and wrist-drop alone in 1 case. The polyneuritis was marked in these cases and the paralysis was usually bilateral. This can be seen in some of the photographs.

Euphoria, a sense of well-being, as described by House, was present in our cases, except in those cases associated with polyneuritis.

Asthenia was present in 100 per cent. of cases and differed in degree. It is one of the symptoms which characterizes the disease. It is with difficulty they can move about in bed, and in some cases they are absolutely powerless. This lasts for a considerable period after convalescence has been established.

Reflexes were exaggerated in 13 cases, normal in 4 cases and decreased in 3. They are not constant and varied with the stage of the disease. In the early stages almost all were increased. As the lethargy developed they gradually decreased and returned to normal late in the disease.

Kernig's sign was not constant either, although slightly positive in 9 cases. There were stages during the disease when Kernig's sign would be markedly positive, associated with muscular hyper-tonus and later when it would be absent, so that the conclusions drawn are that it is at first absent, increased during early lethargy and decreased as the case gets well.

Babinski's reflex was conspicuous by its absence, it was not present in any one single case and was looked for all through the course of the disease.

Muscular atrophy was only seen in those cases which developed polyneuritis or paralysis.

Incontinence of urine and feces were noted in 4 cases, and then only during deep lethargy.

Spinal fluid, it is interesting to note, was disturbed very little in our cases, although other writers, such as Barker, Strauss, etc., found an increased cell count and increased globulin content. We were able to make analysis in only 11 cases, this being due mainly to the fact that most of them were private cases, and great objection was made by their families to lumbar puncture. The analyses of the spinal fluids shows in each case perfectly clear fluid, no sediment on standing, no increase in globulin content, and came out usually under normal or slightly increased pressure. Spinal fluid Wassermann was negative in all and cell count averaged between seven cells per cubic millimeter, which was the lowest count, and thirty-six cells per cubic millimeter, the highest count.

Complete blood analyses were made in 9 cases. Varying degrees of anemia were noted, the lowest hemoglobin count being 40, the highest 96. Red cells ranged from 2,500,000 to 4,200,000. Blood Wassermann was negative. In all there was slight leukocytosis. 7900 to 14,600. Differential count showed polymorphonuclear increase ranging from 62 per cent. to 83 per cent.

Urine was negative except for a slight trace of albumin in 6 cases. Sugar, casts, acetone and diacetic acid were negative. Functional tests when done gave negative results.

Duration of the Disease.—It is impossible to state as yet the exact duration of this disease, as many of these cases are still running their course and are by no means well. The chart will give a fair idea of the length of time these cases run, for example: The shortest case was four days, ending in death at that time; the longest one hundred days, and still the disease is in evidence.

Prognosis.—Of the 20 cases 15 are improving, 1 is well, 1 is dangerously ill and 3 died. Death in these cases was due to respiratory failure. In 3 there were complications, namely:

Case 1. Marked gangrene. The most severe we have ever seen, of toes of both feet, probably trophic in nature. Also lobar pneumonia.

Case 6. Developed otitis media.

Case 19. Developed pneumonia.

In only 4 cases so far has a sequela been found (Case 1, a very marked nystagmus of both eyes, and in the other 3 cases paralysis of eye-lids and extremities).

Conclusions. We believe from our study of these cases that in any case presenting fever, cranial nerve paralysis, particularly the third and seventh nerves, accompanied by stupor or lethargy, with muscular fibrillation and tremor, together with mask-like face, a diagnosis of epidemic encephalitis should be seriously considered.

We have found the spinal fluid practically normal in all cases, but believe a spinal puncture should be made when possible to exclude

cerebrospinal and tuberculous meningitis, anterior poliomyelitis and cerebrospinal syphilis.

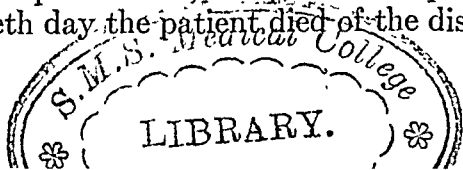
There are many other conditions that may be confused with this disease, yet we feel that cases of acute encephalitis, as we have seen them, are so characteristic and have so uniformly the same symptom-complex that the diagnosis can easily be made by one who has once seen the disease. Other writers speak of mild, ambulatory or abortive cases when there would be considerable difficulty in establishing a diagnosis, but we have not seen any of these cases. We wish to express our appreciation to our colleagues who so courteously and willingly coöperated with us in studying and following up these cases, namely, Dr. H. L. Whitney, of Plymouth; Dr. S. H. Rynkiewicz, Kingston; Dr. Vivian Edwards, Edwardsville; Dr. M. C. Rumbaugh, Dorranceton; Dr. J. W. Kirschner, Luzerne; Dr. John J. McHugh and Dr. R. S. Woehrle, Parsons; Dr. Richard J. Burke, Miners Mills, and Dr. Walter Davis, of Wilkes-Barre, Pa.

The photographs and lantern slides of these cases were carefully made by Dr. S. H. Rynkiewicz, who devoted much time and labor, often under great difficulty in order to secure these photographs.

Report of a severe case complicated by gangrene. (Brief notes.)

Patient, Mrs. R. H. W., married six years, one child, aged thirty-five years.

Patient was taken with a sudden high temperature of 103.5° ; severe headache and painful sore-throat; culture of throat showed hemolytic streptococcus, short chain type; throat had false membrane over tonsils; pains in extremities, especially of legs and arms; fifth day—marked purpura; eruption over legs and arms, trunk, neck and face free. Patient refused to eat, nasal tube used for feeding; irritability of muscles of arms and legs; extremely tender over course of nerve trunk; muscular twitching of hands resembling trembling in paralysis agitans; marked flexion of wrists similar to wrist-drop. Patient restless; cries out; insomnia, delusions ptosis of eyelids. Patient became very drowsy, sleepy, lethargic, and could only be aroused by talking to in a loud voice; answers rational; said she felt better. There was a slight internal squint; partial paralysis of third nerve; partial paralysis of muscles of deglutition; reflexes greatly exaggerated. No Babinski; no Kernig; marked polyneuritis of arms and legs. Patient lethargic until twentieth day, when temperature dropped; patient became brighter; hopes are entertained for recovery. Patient remained in this condition for four days when paralysis of muscles of the lower jaw became more severe; no rigidity of muscles; feet showed toe-drop. Twenty-eighth day patient developed paralysis of epiglottis and inspiration pneumonia; temperature rapidly soared to 107.8° , and on thirtieth day the patient died of the disease.



Purpura cleared up on twelfth day of the disease but was followed by a marked polyneuritis; this was followed by marked atrophic changes of lower extremities, causing blebs filled with serum over the dorsal of both feet together, with gangrene of all toes, which remained until the end.

Physical Examination. Shows mask-like appearance of face partial paralysis of both eyelids; dropping of jaw; paralysis of muscles of deglutition. Reflexes exaggerated; marked flexion of wrist and foot; marked purpura of legs and arms, tenderness along the nerve trunks (polyneuritis). Right facial paralysis.

Report by Dr. George W. Carr of eye-grounds reveals no choked disk; no albuminuric retinitis. Eyes react to light and accommodation. Ear and mastoid region negative. Nose shows deflected septum. No Kernig; no Babinski; no clonus; marked irritability of muscles; delusions marked at times and at other times perfectly clear. Urine reports negative, except for slight amount of albumin. Blood analysis showed a marked secondary anemia, with slight leukocytosis. Widal and blood Wassermann negative. Spinal fluid showed no increased pressure, no cloudiness upon standing, perfectly clear, no increase in globulin, cell count 12 per cm.; spinal fluid Wassermann negative; blood and spinal fluid culture, negative.

Culture from the throat gave a hemolytic streptococcus.

Dr. George Morris Piersol, of Philadelphia, saw this case in consultation.

ACUTE EPIDEMIC ENCEPHALITIS (TWENTY CASES). MOST PROMINENT SYMPTOMS. AGE NINE TO SEVENTY-EIGHT YEARS.

SEX: MALES, TWELVE; FEMALES, EIGHT.

Headache	100	per cent.
Lethargy	100	"
Muscular fibrillation	100	"
Asthenia	100	"
Cranial nerve paralysis	100	"
(3d nerve 90 per cent. = 7th N. 75 per cent. = 5th N.	45	"
Ataxia	90	"
Parkinson's mask	95	"
Delirium	85	"
Catatonia	80	"
Insomnia	80	"
Double vision	75	"
Restlessness	65	"
Reflexes increased	65	"
Choreiform movements	55	"
Polyneuritis	45	"
Kernig's sign	45	"
Paralysis of arms and legs	25	"
Average duration of fever	7	days
Eruption	15	per cent.
Mortality to date	15	"

RECURRENT TYPE I PNEUMONIA: SERUM TREATMENT OF TWO ATTACKS ONE MONTH APART:*

BY HENRY M. THOMAS, JR., M.D.,
BOSTON, MASS.

As an illustration of several important points in the immunology and therapy of lobar pneumonia the following case is reported: Opportunity for complete investigation of the condition was not afforded, but enough data are on hand to make an interesting study.

Our knowledge of immunity—active or passive—in lobar pneumonia is still in a comparatively indefinite state.¹

1. Does one attack confer any immunity?
2. Are successive attacks more liable to be caused by a pneumococcus of a different type or of the same type?
3. Does prophylactic inoculation with killed cultures produce immunity?
4. Can passive immunity be produced by the injection of anti-pneumococcus horse serum?

The blood of patients recovering from lobar pneumonia was shown² to possess, at the time of crisis and shortly after, the power to protect laboratory animals from lethal doses of the type of pneumococcus which caused the pneumonia. Specific antibodies, agglutinins³ and opsonins⁴ have been similarly demonstrated, but their demonstration, in some cases, becomes impossible within a relatively short time after recovery. Skin tests using bacterial antigens⁵ have been tried but are as yet unsatisfactory. Complement-fixation tests⁶ have not added to our information and no one has shown the presence of true pneumotoxin and antitoxin.⁷ These statements show quite clearly that we obtain no practical aid from laboratory methods in demonstrating more than a fleeting immunity to lobar pneumonia following recovery.

Available information as to immunity afforded by an attack is extremely limited. That people have repeated attacks of pneumonia is well known, but the opportunity for studying several attacks in one individual is rarely offered, so that the degree of active immunity produced by one attack is still undetermined. A case in the Rockefeller series⁸ is known to have suffered from sixteen attacks of pneumonia, the last two attacks being studied in the Hospital of the Rockefeller Institute. The bacteriologic history begins with the twelfth attack (1916), which is reported to have been caused by *Pneumococcus* Type I. The next attack (1916) was caused by *Pneumococcus* Type III and the fourteenth attack (1916) by *Pneumococcus* Type IV. During the fifteenth (1916) and sixteenth

* From the Pneumonia Service, Boston City Hospital.

(1917) attacks *Pneumococcus* Type III was isolated. At the time of the last attack of pneumonia he also suffered from acute double otitis media, with cervical and submaxillary lymphadenitis. He was again admitted a year later (1918), suffering from chronic ethmoiditis, left; chronic sphenoiditis, left; acute otitis media, left; acute cervical adenitis, left. He received inoculations of heat-killed pneumococcus vaccine, including the three fixed types, in 1916, after his fifteenth attack and again at the time of his last admission. He has not had pneumonia since February, 1917.

This patient had five attacks of lobar pneumonia within a period of a little more than one year—three of these attacks were caused by the same organism, *Pneumococcus* Type III, which may have been harbored in an infected sinus. That he recovered from sixteen attacks of lobar pneumonia suggests some degree of immunity, but obviously not enough to prevent the attacks.

The only other patient observed in two attacks of pneumonia at that clinic⁸ was a man who had a *Pneumococcus* Type I infection of the right lower lobe in March, 1918. He was treated with serum and recovered uneventfully. About one year later he returned with a typical right lower lobar pneumonia, again *Pneumococcus* Type I. He was desensitized, treated with serum and again recovered.

From February, 1919, when the pneumonia service was started at the Boston City Hospital, to May 1, 1920, there have been two cases other than the one reported in this paper, admitted twice with lobar pneumonia.

M. G., aged twenty-four years, admitted May, 1919; lobar pneumonia, *Pneumococcus* Type II; readmitted October, 1919; lobar pneumonia, *Pneumococcus* Type I.

F. P., aged seven years; admitted May, 1919; lobar pneumonia, *Pneumococcus* Type IV followed by pleural effusion; readmitted September, 1919, with lobar pneumonia, *Pneumococcus* Type II atypical.

No definite conclusions can be drawn from these four cases.

The efficacy of prophylactic inoculation, on the other hand, has been well demonstrated,⁹ and from this fact we may infer that recovery from an attack leaves a certain immunity, the points in doubt being its degree and duration. An attack of typhoid fever usually produces complete and lasting immunity, whereas prophylactic inoculation must be repeated every few years. Arguing from analogy, an attack of lobar pneumonia should produce a much more satisfactory immunity than prophylactic inoculation, or, in other words, a very fair degree of immunity.

Blake and Cecil,¹⁰ announcing the titles of their articles to appear in the coming numbers of the *Journal of Experimental Medicine*, speak of Paper V, "Active Immunity against Experimental *Pneumococcus* Pneumonia in Monkeys following Vaccination with Living Cultures of *Pneumococcus*," and Paper VI, "Active Immunity Following

Experimental Pneumococcus Pneumonia in Monkeys." They evidently have been able to demonstrate active immunity following an attack of lobar pneumonia in monkeys as well as after prophylactic vaccination. This agrees with the current opinions on the subject of immunity in lobar pneumonia in man, and it is, as far as we know, the nearest approach to an actual demonstration that has been brought forth.

Lastly, that Type I, lobar pneumonia, may be aborted and cured by intravenous administration of Antipneumococcus Type I horse serum¹¹ is proof of the production of passive immunity. How long does this passive immunity last? For an absolute answer to this question the substance producing the immunity should be known and tested for until its disappearance from the blood stream. (The question of local immunity need not be discussed at this time.) Agglutinins, precipitins, opsonins and bacteriotropins are shown to disappear rapidly, but the exact duration of their presence in the serum has not been carefully worked out. Whether the curative effect of anti-pneumococcus serum depends on one or all of these factors,¹² or even others yet undescribed, is still a matter of conjecture; therefore the duration of passive immunity for pneumonia must at present remain undetermined. If we turn to a condition in which passive immunity has been carefully studied, *i. e.*, diphtheria, we see that this immunity diminishes very rapidly, so that it cannot be demonstrated at the end of four weeks.¹³ There is no evidence that passive immunity to pneumonia lasts any longer than this. We fully realize the unreliability of this comparison, however, as a toxin-antitoxin mechanism in pneumonia has never been conclusively shown.

RECORD OF CASE.

J. B. Aged twenty-nine years; married; colored; meat handler. *Admitted.* November 29, 1919.

Complaint. Cough, pain in chest.

Family History. Unimportant; wife and one child living and well; no miscarriages.

Personal History. Measles, mumps, whooping-cough and chicken-pox in childhood. Malaria nine years ago. Lobar pneumonia, left upper lobe (no bacteriology), April 19, 1918, in Boston City Hospital. Wassermann positive, April 30, 1918.

Nocturia. One to two times for past six months.

Venereal. Denied.

Habits. Coffee, two to three cups daily. Whisky, two to three drinks; beer, three or four drinks daily before prohibition. Tobacco, chews twenty cents worth a week.

Weight. Best 175 pounds, three months ago. Average, 165 pounds. Last weight, 166 pounds.

Present Illness. Sudden onset yesterday, November 28, 1919, with chill, pain in left side, severe malaise and bone aches. Cough with brown, sticky sputum. Last night vomited and developed "pleurisy pain" in the left chest.

Physical Examination. Well-developed and nourished colored man, complaining of severe pain on inspiration.

Lungs. Slight dulness below left clavicle. In this region and high in the left axilla breath sounds are bronchovesicular in quality, whispered and spoken voice sounds are increased and following cough there are persistent medium rales.

November 29. Wassermann strongly positive. Blood culture positive, *Pneumococcus* Type I. Sputum, mouse inoculation, *Pneumococcus* Type I. Skin test (horse serum), negative.

November 30. 11.30 A.M., 1 c.c. horse serum intramuscularly. 12.30 P.M., 100 c.c. antipneumococcus serum, Massachusetts State Board of Health Laboratory No. 50, given intravenously very slowly. 1.15 P.M., ten minutes after completion of serum treatment, patient developed a diffuse urticaria which was easily controlled by adrenalin, $\frac{1}{1000}$ solution Mx followed in fifteen minutes by adrenalin $\frac{1}{1000}$ solution Mvii.

December 1. Temperature normal; signs in chest slightly more marked than yesterday. White count, 20,200. Roentgen ray of chest: left diaphragm higher than right; left apex dense homogeneous shadow; pneumonia. Urine: albumin, slightest possible trace; sediment, few white blood cells.

December 2. Lungs clearing rapidly, temperature remains normal.

December 3. White count 5800.

December 4. Urine: albumin, 0; sediment, 0; Wassermann negative.

December 6. Lungs clear. Up and around ward. White count 7400.

December 8. Two nights ago patient complained of slight itching. There were a few urticarial wheals to be made out.

In other respects condition is absolutely normal. Patient insists on going home on account of illness of wife. To continue convalescence at home. Discharged cured.

Diagnosis: Lobar pneumonia, left upper lobe. *Pneumococcus* Type I.

From subsequent questioning it was learned that the patient remained quietly at home for several days, but felt so well and strong that about December 12 he returned to work in a meat market, which was damp and cold.

Second Admission. Admitted December 30, 1919 (thirty-one days after preceding admission).

Present Illness. Sudden chill while at work yesterday. December 29, slight headache and general malaise, cough with yellow sputum, which became reddish this morning. Vomited once.

Physical Examination. Over right upper lobe percussion note is dull; breath sounds are tubular; voice sounds tubular and nasal in quality. Few medium rales at left apex.

December 30. Sputum *Pneumococcus* Type I, *Bacillus influenza*. Blood culture, negative. Wassermann strongly positive.

December 31. White count 18,800.

12 M. Skin test (horse serum), very slightly positive (?). 1 P.M., 1 c.c. horse serum intramuscularly. 2 P.M., 100 c.c. Antipneumococcus Type I serum, Massachusetts State Board of Health Laboratory No. 51, administered intravenously, the first 30 c.c. given slowly over a period of thirty minutes and the remainder in fifteen minutes. No immediate reaction was noted during treatment, but twenty minutes later patient had a mild chill and complained of slight itching.

December 31. Roentgen-ray of chest; dense shadow localized in right axilla. Temperature fell during afternoon and night, reaching 99° rectal at 5 A.M. (January 1, 1920), but rose again to 103° rectal at 9 A.M.

January 1. 10 A.M. 100 c.c. Antipneumococcus Type I serum (Laboratory No. 51) given intravenously; no immediate reaction; no chill.

January 2. Temperature, pulse and respiration fell gradually, reaching normal this morning. Patient looks and feels much better.

January 7. Lungs clear. Patient up one-half hour.

January 11. No signs of serum sickness, condition excellent.

January 11. Patient insists on going home. Has not had any evidence of serum sickness. Discharged cured.

Diagnosis: Lobar pneumonia in right upper lobe. *Pneumococcus* Type I and *Bacillus influenza*.

Patient has moved from former address since being discharged and has been lost track of. The question as to whether he ever had any serum sickness following his second pneumonia serum-treatment cannot be answered.

Discussion. Here, then, is a case of recurrent pneumonia Type I, the second attack occurring twenty-nine days after recovery from the first. The infecting organisms may quite possibly have remained in the patient's mouth during the period between the attacks.¹⁴ He was, however, susceptible to a second attack within a month of the first one. To be remembered, in the consideration of this point, is the fact that the first attack was cut short on the third day of the disease by serum treatment. This unquestionably lessened the antigenic value of the first attack and minimized any active immunity which may be acquired in this manner. On the other hand the passive immunity obtained from the horse serum which enabled him to recover promptly from the first attack was not sufficient one month later to protect him from a second attack.

Another interesting phase of this case is the lack of sensitiveness

to horse serum which the patient showed thirty-one days after receiving 100 c.c. of horse serum intravenously.

Longcope and Rackemann¹⁵ in studying 25 cases treated with horse serum made the observations that in cases which escaped serum disease, precipitins and anaphylactic antibodies were not observed, whereas the skin reaction made its appearance irrespective of the amount of serum administered or the method of administration, and appeared whether or not serum disease developed. The skin hypersensitiveness became demonstrable much later, however, in patients who did not develop serum sickness than in those who did, and was first observed in one such case on the thirty-third day and in another on the fiftieth day. They concluded from their observations that serum disease depends on a reaction which takes place within the cells of the body and following which antibodies for horse serum are extruded into the circulation in great quantity. These antibodies dispense with the circulating antigen more or less rapidly.

We see, then, that if serum disease does not develop the circulating antigen may remain for a much longer period and the appearance of circulating antibodies be much delayed or reduced in amount.

Our case differs from their three cases, which escaped serum sickness, in that he did show six days after receiving the first dose of serum a few urticarial wheals. But in view of his subsequent freedom from sensitiveness we feel that it is not safe to place too great reliance on this observation, inasmuch as in the course of making routine ward notes another type of cutaneous lesion may have been mistaken for slight urticaria due to serum sickness. During the twelve days that the patient was under observation following his second course of treatment no sign of serum sickness was noted at any time. No subsequent history is obtainable. We explain his lack of sensitiveness, then, as due to his failure to react in the usual manner by having serum sickness. It is probable that sensitiveness would have developed in a longer period of time.

Conclusions. The development of any active immunity by an attack of lobar pneumonia Type I. may be prevented in part or entirely by the early administration of antipneumococcus serum Type I.

Passive immunity obtained from antipneumococcus horse serum Type I may not protect against an attack of pneumococcus Type I pneumonia for more than one month.

Sensitiveness to horse serum is occasionally late in developing; therefore serum treatment of a patient who has recently received serum should not be omitted through fear of anaphylaxis without first testing the patient's degree of sensitiveness and attempting to desensitize him.

It is interesting to note the occurrence of two strongly positive Wassermann reactions, each while the patient's temperature was

up, whereas one done during the afebrile period intervening was negative. In 1918 his Wassermann reaction was positive when he was afebrile.

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THE COLLOIDAL GOLD CURVE IN EPIDEMIC ENCEPHALITIS: A PRELIMINARY NOTE.*

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THE occurrence of abnormal changes in the reaction of colloidal gold solution to the spinal fluid in epidemic encephalitis has not,

* This paper is based upon cases which have been at Bellevue Hospital, New York, and has been written at the suggestion of Dr. Foster Kennedy, physician in charge of the neurological department. We wish to express our thanks to Drs. Eugene F. DuBois, Robert J. Carlisle, Linnaeus La Fetra, Charles E. Nammack and Van Horne Norris for permission to use reports from their services: We are indebted to Dr. Douglas Symmers for the use of the records of the pathologic laboratory.

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to our knowledge, been recorded up to the present time. In the course of routine examination of cases of this kind in Bellevue Hospital we have noticed the frequency with which variations have occurred. These variations from the normal suggested syphilis, although there were no other serological (Wassermann) or clinical evidences of this disease. On the other hand there were definite signs of encephalitis of the epidemic type. The spinal fluids upon which these tests were made were sent to the pathologic laboratory, in most cases, shortly after admission. The time of admission varied considerably as regards the week of the disease.

Case No.	Observation.	Weeks.	Cells.	Colloidal gold reaction.
1	1st	I	6	—
2	1st	I	14	1112100000
3	1st	I	40	—
4	1st	II	22	—
5	1st	II	0	—
6	1st	II	23	—
	2d	III	?	—
	3d	V	?	0012210000
7	1st	II	10	0000110000
	2d	V	2	0001121100
	3d	XI	2	4221211000
8	1st	II	0	—
9	1st	II	4	—
10	1st	III	4	—
11	1st	III	43	—
12	1st	III	12	—
13	1st	III	95	0001210000
14	1st	III	43	—
15	1st	III	65	—
16	1st	III	30	—
17	1st	III	134	0012231000
	2d	V	3	—
18	1st	III	20	1122100000
19	1st	IV	9	1222100000
20	1st	IV	?	—
21	1st	IV	10	0000110000
22	1st	V	11	—
23	1st	V	40	0000121000
24	1st	V	5	—
25	1st	V	?	—
	2d	XI	?	—
26	1st	VI	1	—
27	1st	VII	?	5432211000
28	1st	VII	30	0001232100
	2d	XIII	2	5544332100
29	1st	VII	?	—
30	1st	VIII	13	—
31	1st	VIII	19	4432110000
	2d	XII	2	0112210000
32	1st	VIII	8	0122110000
	2d	XVI	4	0022110000
33	1st	XI	14	0000110000
34	1st	XI	?	—
	2d	XII	0	—

NOTE.—Dashes indicate zeros.

The accompanying table indicates the number of observations made, the week of the disease and the number of cells found and the type of colloidal gold reaction. In a few cases more than one observation is recorded. The cases included are not all those admitted to Bellevue Hospital but only those in which colloidal gold tests were done.

In conclusion, we have been unable to observe any relation between the colloidal gold curves noted and the severity, duration or clinical picture of the disease. However, it does appear that in a large percentage (41 per cent.) of cases of epidemic encephalitis chemical changes, whether parenchymatous or meningeal, are present in the central nervous system which produce substances in the spinal fluid able to bring about an abnormal colloidal gold reaction.

It has been shown that in other conditions involving changes in the central nervous system alterations in the reaction of colloidal gold to the spinal fluid are analogous to those just described as occurring frequently in epidemic encephalitis. *Abnormal colloidal gold reactions are evidence of pathologic changes and not of specific etiology.* The diagnosis of etiology by means of the colloidal gold reaction cannot be made without confirming clinical evidence based upon the progress and symptomatology of each case.

CARCINOMA OF THE SUPRA-AMPULLARY PORTION OF THE DUODENUM.

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CARCINOMA of the duodenum may be classified according to position. Clinically the most valuable classifications depend on the relation of the tumor to the ampulla of Vater. Pic¹ speaks of carcinoma of the duodenum as being parapyloric, periampullary or prejejunal. Fenwick² and Bland-Sutton³ classify the growth as supra-ampullary, ampullary or infra-ampullary. The latter grouping is probably the more valuable.

Carcinoma of the duodenum is a rare condition. According to autopsy figures cited by Max Müller,⁴ Perry and Shaw,⁵ Ruepp,⁶ Nothnagel,⁷ Tieman⁸ and Fritz Müller⁹ the average incidence is about 0.035 per cent. Of 4177 cases of carcinoma of the intestine

collected by Jefferson,¹⁰ 130, or 3.1 per cent., were in the small intestine. Brill¹¹ gives a somewhat lower figure. The proportion of duodenal to jejuno-ileal carcinoma varies with different authors, but a large series of cases show that the two are about equally divided in point of frequency. Involvement of the ampullary region is the most common form of carcinoma of the duodenum; supra-ampullary carcinoma is the next most frequent and infra-ampullary rarest. Averaging the figures quoted by Perry and Shaw,⁵ Fenwick,² Geiser,¹² Forgue and Chauvin¹³ and Rolleston,¹⁴ 24 per cent of duodenal carcinomata occur in the supra-ampullary portion, 64 per cent. in the ampullary portion and 12 per cent. in the infra-ampullary portion.

The relation of supra-ampullary carcinoma to a preceding duodenal ulcer is much disputed. Ewing¹⁵ points out this relationship. Jefferson¹⁰ has collected 30 cases of carcinoma arising in old duodenal ulcers. But certainly carcinoma of the supra-ampullary portion of the duodenum may occur independently of ulcer. Judd¹⁶ says "there is little definite evidence that carcinoma of the duodenum ever arises from an ulcer." Good general reviews of the subject of carcinoma of the duodenum are given by Heulin,¹⁷ Geiser,¹² Deaver and Ravdin,¹⁸ Brill¹¹ and Forgue and Chauvin.¹³ The last two mentioned give very complete bibliographies.

We wish to report the following case:

Charles S., aged seventy-eight years; colored; laborer; admitted on the service of Dr. T. R. Boggs, January 28, 1920. Medical No. 6530.

Complaint. "Sore-mouth; upset stomach."

Family History. Unessential.

Past History. Good general health up to about 1918, when he began to note weakness and lessened ability to work. Constipated since 1918. No melena nor bloody stools. Gonorrhea several times. Genital sore many years ago. No secondaries.

Habits. Unessential.

Weight. Average, 135 pounds. Thinks he has lost 20 pounds in the last year.

Present Illness. Onset about November 15, 1919, with productive cough and weakness. No hemoptyses, but at times there has been blood-streaked sputum. The weakness became progressively more marked until about January 1, 1920, when the patient was forced to take to his bed. There has been fairly constant, slight nausea and for the past two weeks he has eaten very little. Since January 1, 1920, there has been frequent vomiting of small amounts of material; none recognized, however, as food eaten on the previous day. For the two months preceding there had been extreme constipation. No abdominal pain.

Physical Examination. Patient is an emaciated, elderly negro. Teeth represented by a few old snags. Buccal mucosa ulcerated

opposite one such snag. Tongue is heavily coated with a white fur. Breath very foul. No glands palpable above the left clavicle.

Maximal supraclavicular and infraclavicular retraction. Slight respiratory lag over left upper chest. Impairment over both upper fronts, where breath sounds are harsh and expiration prolonged. No rales. In back there is impairment at the left upper shading to almost complete flatness in the left midinterscapular area. Breath sounds here have a distant tubular quality and there are many fine moist rales. Whispered voice accentuated in suprascapular fossa. Heart clear. Slightly increased retromanubrial dulness. Vessel walls markedly thickened, with some calcification. Blood-pressure, 80 to 50.

Abdomen scaphoid. Huge, right inguinal hernia, which has encroached upon the abdominal wall. Abdomen held very rigidly. No tenderness or local spasm made out. Liver and spleen not felt. No masses. At a later examination the patient was put into a warm bath and the abdomen palpated. A sense of resistance in the epigastrium was made out, but no definite outline could be felt.

Testicles atrophied. No genital scar. Prostate large, soft and homogeneous. Rectum negative.

Ophthalmoscopic examination shows normal fundi.

Laboratory Findings.

Blood. Red blood cells, 3,048,000. White blood cells, 5750. Hemoglobin (Sahli), 45 per cent.

Differential formula showed a slight polymorphonuclear leukocytosis.

Urine. Sp. gr., 1.010 to 1.015. Persistent trace of albumin. Granular casts.

Sputum. Positive for tubercle bacilli.

Stool. Bile present. No ova or parasites. Positive for occult blood. (Benzidine and guaiac tests.)

Test-meal. 100 c.c. of brownish fluid. Bile, 0. Lactic acid, 0. Test for occult blood strongly positive. (Benzidine and guaiac tests.) No Oppler-Boas bacilli. Free HCl, 17 per cent. Combined, 16. Total, 33.

Wassermann. Negative.

Roentgen-ray Report (Dr. J. W. Pierson).

Chest. Marked spotty infiltration, both uppers, more extensive on the left than on the right; tuberculous in origin.

Gastro-intestinal Series. Stomach lies low in the pelvis; marked filling defect in region of antrum pylori, probably due to pressure from lumbar spine; pylorus intact; no retention; duodenal cap well filled. Due to weakness, the patient could not be fluoroscoped.

Course in Hospital. Patient became progressively weaker. He vomited small amounts of fluid material at times. His chief complaint was difficulty in swallowing, but since a stomach-tube passed easily this was thought to be due to a reflex cardiospasm rather than

to an organic esophageal obstruction. On the night of February 10 he showed active delirium. On February 11 he sank into a semi-comatose state and died February 12.

Clinical Impression. Ulcerative pulmonary tuberculosis. Carcinoma of the stomach. Secondary anemia.

Autopsy, No. 1592. *Anatomic Diagnosis.* Chronic fibroid pulmonary tuberculosis, with bronchiectasis; ulcerative tuberculous enterocolitis; conglomerate mass of tubercles in the wall of the aorta; generalized miliary tuberculosis; adenocarcinoma of the duodenum; thrombosis of the right common iliac and right pulmonary arteries, left common iliac vein and prostatic veins; arteriosclerosis; right inguinal hernia; undescended testicle, right; brown atrophy of the heart.

Stomach and Duodenum. The stomach is moderately distended with gas and fluid, especially the pyloric portion. The duodenum, just beyond the pylorus, is enlarged and a dense mass can be felt in it, apparently entirely filling the lumen. The serous surfaces of the stomach and duodenum are smooth and glistening.

When opened the stomach shows no changes. A finger can be readily introduced through the pyloric orifice, but the opening is eccentrically placed and a firm mass can be palpated in the duodenum, completely encircling the finger.

This mass is a large, oblong, solid, polypoid tumor, attached to the inferior wall of the bowel and arising just beyond the pylorus. It measures 6 x 5 x 3 cm. in its greatest diameters. The base is somewhat smaller than this.

The surface of the tumor is smooth and rounded, with small hemorrhages here and there. The upper surface is hollowed out into a deep gutter with steep sides, which gradually taper as they extend upward, and conforming to the curve of the bowel wall they overlap above, forming a tunnel through which the gastric content passed. It was into this tunnel that the finger readily entered. When the bowel was opened these margins sprang apart.

The tumor is grayish white in color and cuts with some resistance. The cut surface is rather homogenous in appearance and is dotted with a few yellow flecks. The growth seems to penetrate only a little way into the wall of the bowel.

The duodenal mucosa is gray and translucent, and is reflected for a short distance upon the base of the tumor. The folds of the mucosa are well defined and prominent. The ampulla of Vater is negative.

The regional lymph glands are not enlarged and there are no metastases visible in the liver.

Microscopic Examination. The tumor is composed of columnar epithelial cells, having a definite glandular arrangement. Often these cells are heaped up into several layers. There is an abundant and rather dense connective-tissue stroma in which are many

capillaries, and which is infiltrated with small round cells, plasma cells and leukocytes. The gland-like spaces enclosed by the epithelial cells are frequently filled with leukocytes. Small areas of necrosis are seen.

At the base the rather orderly adenomatous arrangement is lost, and the cells are more irregular in size and shape and grow in solid cords, penetrating into the circular layer of muscle. Mitoses are fairly numerous. The mucosa can be traced upward upon the tumor for a short distance, then it ends abruptly.

In appearance and arrangement the tumor cells resemble more closely those of the glands of the mucosa than those of Brunner's glands.

In none of the sections of the regional lymph glands could any metastases be found. Sections of the liver and pancreas were likewise negative for metastases.

Discussion. The diagnosis of supra-ampullary carcinoma of the duodenum is surrounded by great difficulties. In fact, Geiser,¹² in 1907, stated that he had been unable to find a case in which the diagnosis had been made *ante mortem*. Most of the cases have been erroneously diagnosed as carcinoma of the pylorus. As can be easily seen, carcinoma at the pylorus and supra-ampullary carcinoma of the duodenum may well give the same symptomatology. Symptoms of weakness, dizziness, emaciation, anemia and the like, referable to the state of carcinoma cachexia, are as common to the two conditions as are the more local symptoms, such as anorexia, flatulence and vomiting. The intestinal symptoms of supra-ampullary carcinoma are not at all typical, melena being the most common. Constipation is the rule. If there is obstruction from either cause there will be dilatation of the stomach and consequent vomiting.

Herz¹⁹ says that the gastric contents in cases of duodenal stenosis, due to supra-ampullary obstruction, are not to be differentiated from the contents in pyloric stenosis. Czygan,²⁰ however, states that in duodenal stenosis, due to carcinoma, one is liable to get a high HCl content, but he speaks of duodenal carcinoma in general and does not localize the tumor. In the case he cites, one of supra-ampullary involvement, there was 35 per cent. free HCl. Friedrich²¹ gives two cases of duodenal carcinoma occurring between the pylorus and the ampulla, where the absence of a palpable tumor and the presence of free HCl led to a preoperative diagnosis of a benign pyloric stenosis. Ewald,²² Wurm²³ and others cite cases without free HCl and with lactic acid. Friedenwald,²⁴ in a series of 1000 cases of carcinoma of the stomach states that 89 per cent. show an anacidity and a further 3 per cent. show a hypochlorhydria; 82 per cent. show lactic acid. This author also points out that anacidity is an early finding in gastric carcinoma. Although no hard and fast rule can be laid down as to the presence of free HCl in the gastric contents in cases of supra-ampullary duodenal carci-

noma, it seems safe to conclude that the HCl disappears much earlier in cases of gastric carcinoma than in cases of neoplasm of the duodenum.

Forgue and Chauvin¹³ mention that blood is infrequently found in the gastric contents in cases of duodenal cancer while it is a very common finding in gastric carcinoma. A high grade of indicanuria has been said to be of some help in the diagnosis of duodenal carcinoma if the lumen of the duodenum is occluded.

Pain is an extremely variable symptom, both as to presence and as to location. It usually is not a prominent feature. If present it is more often of a constant, dull, dragging quality, usually referred to the epigastrium. It is more liable to have no relation to meals. The pain may sometimes be paroxysmal in character, due presumably to sudden changes in the degree of distention of the gall-bladder. According to Geiser,¹² icterus may occur as a late manifestation in supra-ampullary carcinoma even though the ampulla be not directly involved.

Most authors agree that the tumor is seldom palpable, although Fenwick² claims that in 60 per cent. of the cases the mass can be felt if it is located near the pylorus. Rosenheim²⁵ states that supra-ampullary carcinoma of the duodenum, if to be felt at all, is to be sought for just a little to the right of the midline and on a sector between the umbilicus and the gall-bladder region. Forgue and Chauvin¹³ explain the rareness of a palpable mass on the basis of the form of duodenal carcinoma. Carcinomata of the duodenum are usually either flat plaques, showing a tendency to annular growth, or are nodules so small that they escape palpation. Judd¹⁶ also points out that duodenal carcinomata are often polypoid in character. What has at times been taken for the primary mass on palpation has later been seen to represent a group of metastases in mesenteric glands. Duodenal carcinoma, in general, does not metastasize readily or early. The most common sites of metastases are in the pancreas, the liver and glands. Enlargement of the supraclavicular glands, especially on the left, have been described, as well as metastases to the vertebræ. The nodules in the liver seldom attain any great size.

From the roentgen-ray standpoint, carcinoma of the duodenum is an almost unknown occurrence. Dr. F. H. Baetjer²⁶ has told us that he has never seen a case. Carman and Miller²⁷ do not mention duodenal carcinoma as such. They say: "Other than duodenal ulcer the only important condition of the small intestine which is readily susceptible of demonstration by the roentgen-ray is obstruction; if near either extremity of the bowel the site of the obstruction can be shown." They give no pertinent picture, however. Judd¹⁶ from the same clinic gives a number of pictures of intestinal obstruction but none would allow of a definite diagnosis of duodenal carcinoma. There was no obstruction in our case. Clinically

the gastro-intestinal roentgen-ray series was essentially negative, although at the time the length of the "stalk" of barium (*C* in Fig. 1) was commented on. This was taken to be the stream of barium passing through the pylorus. The duodenal cap (*D* in Fig. 1) was

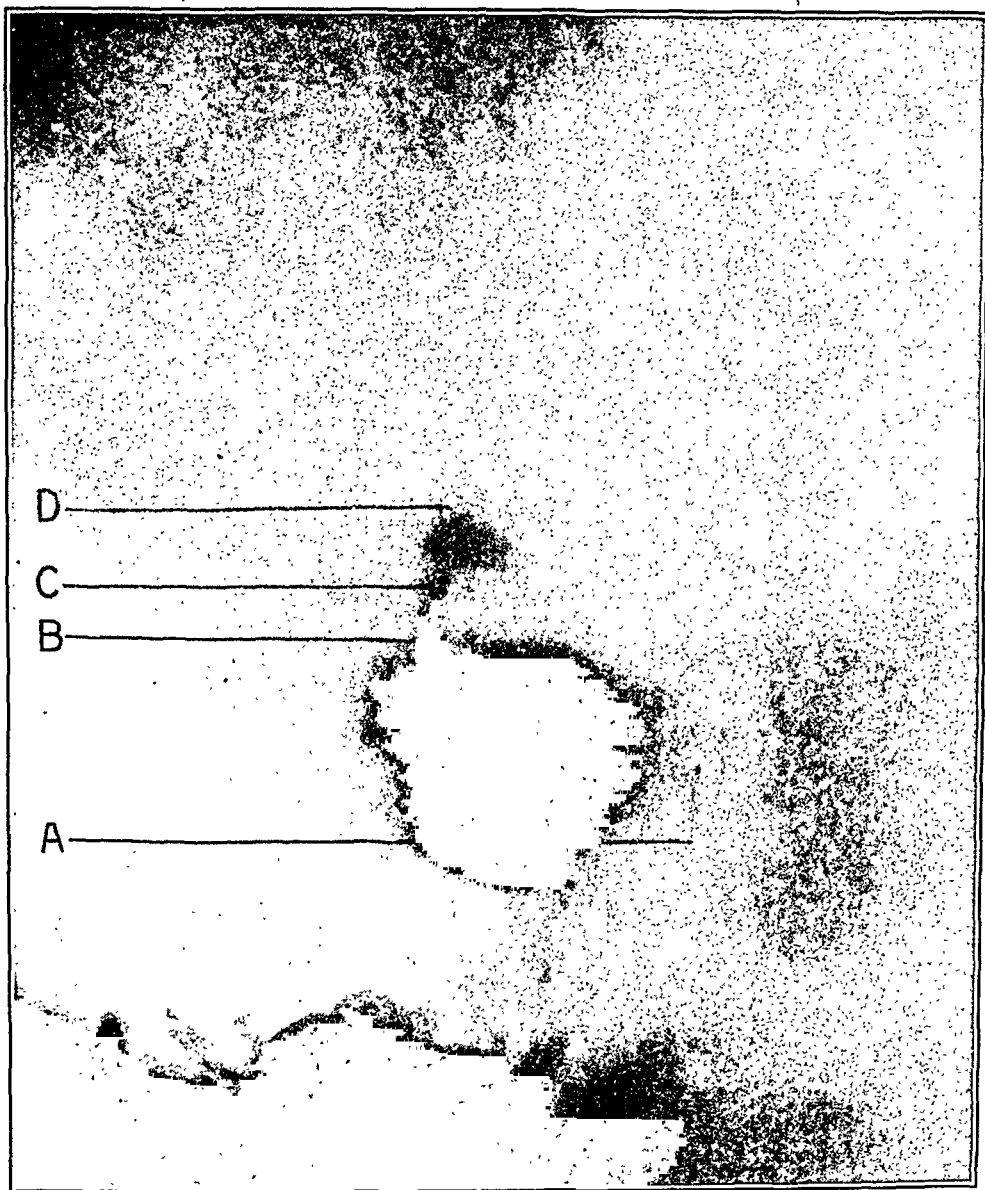


FIG. 1.—Roentgen ray of stomach fifteen minutes after ingestion of opaque meal. *A*, filling defect due to pressure of spine; *B*, pylorus; *C*, stream of barium passing through the lumen formed in the carcinoma; *D*, duodenal cap.

normal. On comparing the roentgen-ray picture with the pathologic specimen the real explanation became apparent. The carcinoma had formed a canal, as it were, through which the gastric contents passed, and this "stalk" represented the stream of barium passing through the lumen of the duodenal growth. Several small, soft



FIG. 2.—Adenocarcinoma of the duodenum. Note the deep gutter on the upper surface of the tumor. P, pylorus; V, ampulla of Vater.

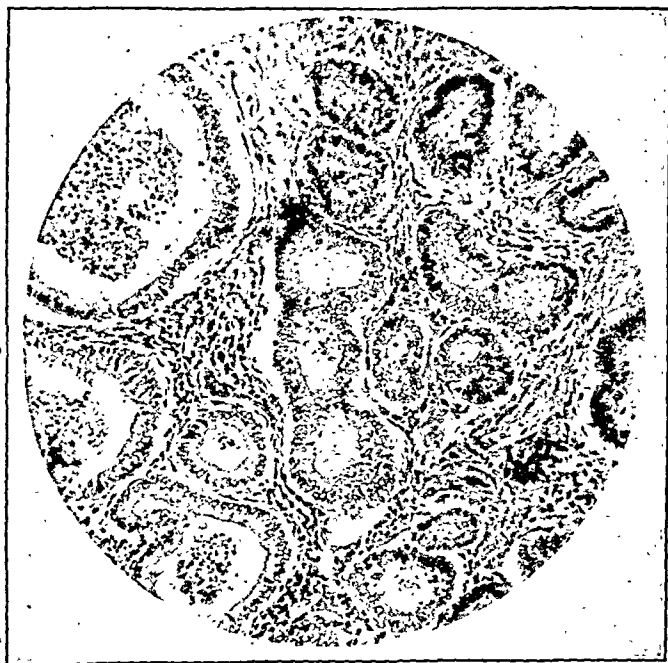


FIG. 3.—Adenocarcinoma of the duodenum. Section showing type and characteristic arrangement of tumor cells and abundant stroma. $\times 125$.

shadows surrounding the stalk are probably due to leakage of barium between the mass and the duodenal wall, since the sides of the carcinoma did not fuse above. This roentgen-ray finding has been thought to be conclusive enough to warrant a strong suspicion of duodenal carcinoma in case another similar picture should present.

Conclusions. The rarity of duodenal carcinoma has been pointed out and the difficulties of diagnosing this condition, when it occurs in the supra-ampullary portion, have been outlined. The persistence of free HCl in the gastric contents, when all other evidence points to a gastric carcinoma, should make one at least think of duodenal carcinoma. In the light of the pathologic findings we believe that a similar roentgen-ray picture, in the future, will strongly suggest a carcinoma of the supra-ampullary portion of the duodenum.

We are indebted to Dr. E. H. Terrill for the photograph of the tumor and for the photomicrograph.

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ETIOLOGY OF ACNE ROSACEA THROUGH A VISCERO-NEUROLOGIC MECHANISM.

BY FRANK PORTER MILLER, M.D.,
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THE causation of acne rosacea as well as many of the other common dermatoses has been more or less a matter for conjecture. So many predisposing factors have been ascribed, and these so variable, that no tangible etiology has been forthcoming. Heretofore any skin disorder without an apparent etiology has been classed as being of a nervous origin, but as our neurologic knowledge increases and becomes more precise, we are able to eliminate a few in the group of the so-called nervous dermatoses.

Disturbances of the peripheral mechanism of vasomotor pathways have been analyzed in a few diseases, including tonic hyperemias (erythromelalgia), a few of the spastic anemias, such as Raynaud's disease, intermittent claudication and vasomotor irritability, as in acute angioneurotic edema, and multiple gangrene of the skin.

The cutaneous disorders offer a lucrative field for investigation, and many etiologic factors which have been clouded with obscurity will unfold if we possess an adequate knowledge of visceral neurology.

For the sake of clarity and also for completeness, I will review the prevailing etiology and symptomatology in as brief a manner as possible. This is essential if the reader is to get a comprehensive conception of our explanation.

Acne rosacea consists of two processes, a rosacea and an acne. The former is a chronic, congestive disorder of the face, particularly of the nose, chin and forehead, characterized successively by flushing, permanent enlargement of the bloodvessels, and in some advanced cases, tissue hypertrophy (rhinophyma). The acne lesions are usually secondary in development. There are essentially three stages of the disease; the first manifestation is a tendency to flushing of the face, which becomes especially evident after eating or drinking stimulating articles or exposure to cold wind or upon entering a warm room. There is a distinct predilection for the middle third of the face, but in the majority of cases the malar regions are also involved. The redness is usually transitory at first. In many cases the condition passes on to the second stage. The frequent repetition of flushing gradually tends to enlargement of the capillaries and venules which now become visibly dilated. They are seen as small tortuous or arborescent vessels on the nose and cheek. The appearance commonly described as brandy nose is now present. Coughing, laughing and mental excitation lead to paroxysmal exacerbations. Acne papules and pustules now usually make their appearance in crops. In exceptional cases the

disease progresses to the third stage, which is characterized by further capillary engorgement and tissue hypertrophy.

Gastro-intestinal disorders, improper diet, inordinate use of tea and coffee and alcoholic beverages, have all been suggested as predisposing factors. Although most dermatologists realize there is a neurogenic element which masks the etiology, the anatomic pathways have never been suggested.

There is no true acne rosacea, as we will attempt to prove in the following paragraphs, and to get the correct conception we will discuss this from a polyetiologic viewpoint.

Vagal and Trigeminal Stimulation. It is universally accepted that gastric stimulation is probably the causative factor in a great majority of cases, and when the stimulation is great enough to evoke a response, the afferent sensory impulse courses through the vagus, the cells of which are situated in the ganglion nodosum and thence to that portion of the dorsal nucleus receiving the visceral fibers. Interconnecting neurons now communicate with the nucleus of the fifth cranial and by antidromic impulses vasodilatation is produced. It has been shown by Stricker and Morat¹ that dilatation of the vessels of the hind limb can be produced by stimulating the posterior roots of the nerve going to the limb, *i. e.*, far below the point of origin from the cord of the constrictor fibers to the same part of the body. This work was widely discredited until later confirmed by Bayliss² for all manner of stimuli. He has shown that stimulation of the posterior roots either before or after they have passed through the ganglia causes dilatation of the vessels in the area of the supply of the roots, whatever be the nature of the stimulus employed, whether electric, chemical or mechanic. This effect is not destroyed by previous section of the posterior roots on the proximal side of the ganglia, showing that the fibers by means of which the dilatation is produced have the same origin and course as the ordinary sensory nerves of the limbs. Since the vasodilator impulses pass along these nerves in a direction opposite to that taken by the normal sensory impulse, Bayliss has designated them as antidromic impulses. In accepting this view we must assume that stimulation of any of the sensory nerves of the body is capable of producing vasodilatation, and sensory nerves are capable of carrying efferent impulses. It is quite possible that antidromic impulses could explain many of the trophic disturbances in dermatology. Since the above holds true for stimulation of the posterior roots of a spinal nerve we have every reason to believe that the same would be applicable in the sensory division of the fifth cranial, as the spinal nerves and the trigeminus have many characteristics in common. Both possess a motor as well as a sensory root. The fibers of the sensory root take their origin from the Gasserian

¹ Starling: Human Physiology, Lea & Febiger, 1915, p. 998.

² Ibid., pp. 998-999.

ganglion, which is in all respects similar to the ganglion of a posterior spinal nerve root. The afferent fibers of the fifth nerve, as they enter the pons, bifurcate like a spinal afferent nerve into ascending and descending branches. Furthermore the sensory portion of the fifth nerve bears the same relationship to the parasympathetic system as the spinal nerves do to the sympathetic.

Gaskell³ accepts the presence of vasodilator fibers in sensory nerves with considerable hesitancy and suggests that sensory fibers probably possess secretory functions. His reasoning is very plausible, and we will produce it in part. The condition of the epithelial cells of the skin is dependent on the integrity of the sensory nerves. Therefore the sensory nerves affect the metabolism of the cutaneous epithelial cells. When the secretory nerve to a gland, such as submaxillary gland, is cut the gland cells atrophy, and when sensory nerves to the epithelial cells have been sectioned, atrophy and glossy skin result. The sensory nerve may be considered to control the metabolism of epithelial cells in a manner exactly comparable to the control of gland cells by their secretory nerve. Stimulation of the chorda tympani causes secretion, and that secretion is accompanied by dilatation of the bloodvessels of the gland, probably due to acid metabolites. This is an acid lymph acting upon the loose adventitia of the small vessels. If stimulation of the sensory nerve causes metabolic changes in the epithelial cells corresponding to those in the submaxillary glandular cells upon stimulation of the chorda tympani, then the formation of acid metabolites would cause dilatation of the bloodvessels of the skin just as in the case of submaxillary bloodvessels. From the physiologic data it is shown that stimulation of any sensory nerve is capable of producing a vasodilatation, but whether the impulses are carried through true vasodilator fibers, acting antidromically, or the sensory nerves assume secretory characteristics, is a matter for physiologists to decide.

This shows that the law of Bell and Magendie is not infallible and offers one of the exceptions to the universal law of forward direction in the mammalian nervous system.

Pottenger⁴ has recently explained hectic flush as it occurs in respiratory diseases through this mechanism; though the manuscript is as yet unpublished, he is kind enough to allow me to quote from it. In cases of pulmonary tuberculosis the stimulation does not limit itself wholly to the area supplied by a fifth cranial, but here we also have stimulation from a sympathetic origin. The afferent impulses from the lung mediate with the cervical spinal nerves particularly the third and fourth segments, and by stimulating the third cervical the pinna of the ear will develop a flush, and in a few cases will become noticeably larger than the opposite organ. The flush as it occurs in the malar region is a vagal-trigeminal mediation.

³ *Involuntary Nervous System*, 1915, pp. 96-97.

⁴ Unpublished manuscript.

Local irritation of the peripheral fibers of the fifth nerve will produce the flush, and it is immaterial whether the stimulation arises from within or without the body. The sensory receptors of the trigeminus are widely distributed over the face, the mucous membranes of the superior and anterior nasal fossa, the frontal and ethmoid sinuses, tentorium cerebelli, teeth, mucosa of the posterior inferior nares, the sinuses of the jaw, dura mater, the mucous membrane of the lips, cheeks, posterior and inferior portion of the mouth and the anterior two-thirds of the tongue as taste buds. It is quite conceivable to me that stimulation of these peripheral fibers over a prolonged period would produce a typical acne rosacea. The warmth of a room is often sufficient to bring this out in many individuals, and in others the slightest friction over the sensory fibers will produce the blush.

Since the physiologists have laid so much stress upon the fact that certain impulses will produce an inhibition of the vasoconstrictor center, I will mention another pathway here, though realizing the probability of its occurring in this instance is quite remote. The afferent sensory impulses course centralward until they reach the medulla and then by intercalated neurons are transferred to the vasoconstrictor center producing inhibition. The vasoconstrictor center sends axones via the descending tracts in the cord which terminate at various levels in the anterior horn of the gray matter in the region from the upper thoracic to the upper lumbar spinal nerves. We also know that in the cervical portion of the sympathetic, dilator fibers are carried which are distributed to the mucous membrane of the mouth (lips, gums and palate) nostrils and the skin of the cheek. These fibers, passing from the vasoconstrictor center, pass as pre-ganglionic fibers to the superior cervical ganglion, and thence as postganglionic fibers to the Gasserian ganglion and are distributed to the buccofacial region in the branches of the fifth cranial nerve.

Psychical Relationship. The psychical side of medicine has been sadly neglected; and because of our indifference, or rather our inability to fathom this particular phase, many new cults have attempted to bridge the space which should have been spanned by medicine, and the laity only too eager to accept a new code have been misled, although these cults smack strongly of quackery. Especially those individuals suffering from some chronic disorder, in which the progress has been slow, or the result ungratifying, have been prone to adopt a new creed and the harm resulting from such a reprehensible practice is rather alarming.

The activity of the psychical centers is particularly interesting in acne rosacea, and it is through their activity that the physiology of blushing is explained; and blushing which is produced by the slightest provocation forms one of the early symptoms of the disease, frequent repetition producing enlarged bloodvessels and

finally tissue hypertrophy. Although the location of the psychical centers is rather indefinite it is assumed that they are located in the midbrain or cortex. When feelings of embarrassment or shame are thrust upon an individual the impulse is transmitted to the psychical centers, thence by intracentral nerve paths, which communicate with the sensory nuclei or the trigeminus, producing a reflex vasodilator effect in the area supplied by the fifth cranial. Concomitant with the phenomena of blushing, other functional disturbances are observed, and these are quite constant in all the emotional states of a depressing nature (mydriasis, hyperidrosis, cardiac palpitation and dryness of the mouth and throat). The act of blushing, apparently simple, resolves itself into an intricate mechanism, and by secondary connector neurons stimulates the respiratory center in the medulla, and by the aid of descending tracts in the cord the motor cells in the sympathetic ganglia of the cervical regions are implicated and mydriasis and palpitation occur. It is impossible to decipher with any degree of certainty the mechanism which is conducive to an emotional state, but it is well to remember that the changes may be of a biochemical nature involving the cells of the cerebral cortex. It has been suggested to me that acne vulgaris could probably be explained in a similar manner and that the awakening of sexual desires at puberty produces a reflex stimulation from the cortex to the sensory nuclei of the trigeminus, and that hypernutrition causes an enlargement of the sebaceous glands. This is a suggestion worthy of thought; but remembering that the endocrine glands probably play a leading part in this particular role, it should be borne in mind that when an impulse reaches the brain or spinal cord there are certain neurons which are more direct and offer less resistance than others, and it is along these paths that the reflex will take place; and we may further assume that these paths of least resistance, as they have been called, are in part preformed and in part laid down by the repeated experiences of the individual, and many of these cases which in the beginning show a transitory flush, easily provoked, will in time assume a permanent reddish hue if stimulation is continued.

Furthermore, I am of the opinion that many of these people possess a tricotonic instability. For quite a period clinicians have accepted vagotonia as a distinct entity, and in this condition I believe we probably have an increased tonus and a lessening of the threshold of response in the trigeminus.

Very little has been said regarding the acneiform eruption, but its presence has been explained for a long period as being due to hypernutrition and is merely secondary manifestation.

REVIEWS

DISEASES OF CHILDREN. By JOHN LOVETT MORSE, M.D., Professor of Pediatrics, Harvard Medical School; Visiting Physician at the Children's Hospital and Consulting Physician at the Infant's Hospital and at the Floating Hospital, Boston. Third edition. Pp. 639; 200 case histories, freely illustrated. Boston: W. M. Leonard, 1920.

THE third edition has been thoroughly revised, but the general plan of presenting the subject through the medium of the histories of actual cases has been retained. Many new cases have been substituted for old ones and in others the diagnosis and treatment have been formulated on more modern lines rather than detailing those that were actually employed. The whole subject of pediatrics is well covered under the usual classification, with a final section for the more rare conditions which do not fall definitely under the "system diseases." This type of book offers one of the best means for practitioners to develop their powers of inductive reasoning, if they will avoid reading the final conclusion until after they have attempted to draw their own inferences. Most noteworthy is the fact that the author reaches his diagnosis chiefly with the aid of clinical observation at the bedside. Nothing could better illustrate the value of trained observation and careful physical diagnosis as contrasted with the too prevalent modern tendency to rely too largely upon laboratory aid, valuable as the latter undoubtedly is.

J. C. G.

AN ATLAS OF THE PRIMARY AND CUTANEOUS LESIONS OF ACQUIRED SYPHILIS IN THE MALE. By CHARLES F. WHITE, M.B., Major, R.A.M.C., Rochester Row Military Hospital, and W. HERBERT BROWN, M.D., late Captain, R.A.M.C., Victoria Infirmary, Glasgow. First edition. Pp. 32; 79 illustrations (photographic) and 4 colored plates. New York: William Wood & Co., 1920.

AN atlas founded upon 19,000 cases of syphilis studied and photographed in a large army venereal hospital. Nine thousand cases of primary sores gave the authors the material to classify ten different types of chancre; a classification entirely new, true to

experience and a welcomed change from text-book reiteration. The idea of making many (51) of the photographs for stereopticon study is novel and highly instructive. The text is brief, succinct, and descriptive, being limited to only an accurate picture of the various lesions, in which you can feel the authors speaking from close personal observation. One hundred and thirty extragenital chancres are studied. In each lesion described the percentage of the frequency of its occurrence is stated, being most valuable as coming from such a large personal series. A. R.

INDEX OF SYMPTOMS. By RALPH WINNINGTON LEFTWICH, M.D.,
Late Assistant Physician to the East London Children's Hospital;
Author of "Tabular Diagnosis," etc. Seventh edition, revised by
H. N. WARNER COLLINS, B.Sc., M.R.C.S., L.R.C.P. Pp. 595.
New York: William Wood & Co., 1920.

THE seventh edition of Leftwich's work has been revised by Collins. The latter has added considerable material to the work so that the present edition is a distinct improvement over former ones. The reviewer finds that as compared with the second edition nearly 200 additional pages have been incorporated in the text. To those who are not familiar with the book, or books of this type, it may be said that symptoms and signs are listed under the various main headings of physical diagnosis. Under these main headings are subheadings of the symptoms relating to the main heading. After the symptoms, in alphabetical order, are arranged the diseases which will produce this symptom. The ones most likely to cause the symptom are starred. In this way one is able to arrive at a diagnosis by methods somewhat different from the ordinary ones in common use; thus if we find that a patient has pain in the chest we look under this heading and find the list of diseases which are associated with pain in the chest. Then we find that he also has cyanosis. The heading cyanosis is consulted and all diseases which are not associated with pain in the chest and with cyanosis are eliminated, while tabulating the diseases which are associated with these two symptoms, pain in the chest and cyanosis. We then take up a third and fourth symptom which the patient presents and tabulate those diseases in which all four symptoms are present. Continuing in this manner indefinitely until we have ruled out all diseases which are not listed under the heading of the symptoms the patient presents we can ultimately arrive at a diagnosis, presumably with a minimum of trouble. The method sounds attractive and easy, but unfortunately it is not always easy to interpret physical signs or properly to evaluate accurately; subjective symptoms described by the patient. J. H. M., Jr.

EATING TO LIVE LONG. By WILLIAM HENRY PORTER, M.D.
Pp. 243. Chicago: Reilly & Lee Company, 1920.

THIS small volume contains twenty-two chapters on various subjects connected with food and diet. The author discusses foods from every standpoint. He explains to us what foods are good and what foods are bad and he gives adequate reasons for his views. Furthermore, he dismisses with a thorough explanation the fallacies of some of the various dietetic delusions with which this subject has been burdened in the past.

The book is written in such a manner as will appeal not only to the physician but will also be classed among the popular medical books which may be read by the layman with interest, not to mention the benefit that he would derive from a study of the context.
J. H. M., JR.

INTERNATIONAL CLINICS. By H. R. M. LANDIS, M.D. Thirtieth series. Pp. 314; 40 illustrations. Philadelphia and London: J. B. Lippincott Company, 1920.

VOLUME 11 of the thirtieth series of these clinics contains eighteen articles on subjects of varying interest. The clinics are interesting and well worth reading. Particular commendation should be given the clinics of Drs. Ashhurst, Thompson, Lyon, Magnuson and Speese. They are well written and authoritative.

J. H. M., JR.

THE DUODENAL TUBE AND ITS POSSIBILITIES. By MAX EINHORN, M.D., Professor of Medicine at the New York Postgraduate Medical School; Visiting Physician to the Lenox Hill Hospital, New York. Pp. 122; 51 illustrations. Philadelphia and London: W. B. Saunders Company, 1920.

DR. EINHORN, in this little work on the duodenal tube, first traces how he developed this instrument from its original model to its present finished state. He then shows for what purpose it may be employed in diagnosis of diseases of the upper alimentary tract, and lastly concludes his work with several chapters on the use of the tube in the treatment of diseases in this part of the body. Full credit should be given to Dr. Einhorn for his development of this device which has proved so useful in diagnosis, and which is so very extensively employed in the present day. It hardly seems fair that more credit is not given to Dr. Einhorn for conceiving, developing and popularizing the tube. Minor modifications in the shape of

the capsule have been made by other individuals which in no way alter the principles of the tube, and because of these minor modifications, the name of the modifier has been applied to the tube as a whole, although these changes have in no sense altered the basic principles of the instrument.

J. H. M., JR.

SURGICAL CLINICS OF CHICAGO. October, 1920. Vol. IV, Number X. Pp. 223; 46 illustrations. Philadelphia and London: W. B. Saunders Company.

THIS number continues the character of work and good reputation of the *Clinics*. It has broadened its scope and increased the number of its contributors, giving the reader articles on the specialties in medicine and surgery. So that there is valuable reading for most of the medical profession.

The case reports are most admirably worked up, and the minutest details presented. In fact the one criticism is that possibly in some instances a little too much space is given to remote family and personal history. The articles on perinephric abscess, lesions, transfusion, kidney infections and hematuria, will be of interest to all surgeons.

E. L. E.

MENTAL DEFICIENCY (AMENTIA). By A. F. TREDGOLD, M.D., F.R.S., Edin. New York: William Wood & Co., 1920. Third edition.

THIS is the third edition of this very important work, and has been thoroughly revised and brought up to date, the chapter on Moral Imbecility having been entirely rewritten. With the exception of this chapter there is no marked difference from the former editions.

From the medicolegal standpoint the chapter on Vicious and Criminal Aments and the following chapter on Moral Imbecility are most satisfactory, for they clarify this very important subject. According to the author, in vicious and criminal aments there is a fundamental inability to develop a moral sense, with the result that serious misconduct is characteristic of their lives. In another type of aments the misconduct is due to weakness of will. The third type consists of those who suffer from morbid impulses. He calls attention to a residue of criminal aments who cannot be thus precisely docketed, for their misconduct depends upon a combination of defects. In many the early upbringing is at fault, for the qualities of moral sense and inhibition have never been developed. In discussing the moral imbecile, the author properly points out that

one reason for the misconception of this group of cases is because the term "imbecile," which has long been applied to an immense degree of mental defect, is entirely unlike that present in these cases. For this reason he prefers the term moral "defective." The best definition of a moral imbecile is that given by the author when he says "these individuals have defective wisdom, with a defect of moral sense." He further points out that moral imbeciles are by no means unintelligent in the ordinary sense, and re-emphasizes the fact that these patients are clever but incapable, that they may have plenty of intelligence but little or no wisdom, and that, as Dr. Mercier pointed out, such an individual is a "clever fool."

Another chapter upon The Criminal Responsibility of Aments is also very instructive. Altogether this is an excellent book.

PHYSICAL BASIS OF HEREDITY. By THOMAS H. MORGAN, Professor, of Experimental Zoölogy in Columbia University. Pp. 305; 117 illustrations. Philadelphia and London: J. B. Lippincott Company.

Of the recent advances in the study of heredity and Mendelism none have been so productive in results as the experimental work of Professor Morgan and his colleagues. About ten years ago they began work with *Drosophila*, the little fruit fly, and this form has turned out to be the most favorable yet utilized in the study of heredity. In *Drosophila* they have already found several hundred factors which exhibit Mendelian segregation; its chromosomes are distinct and few in number; it is both hardy and prolific; it is easily handled in the laboratory, being reared in pint bottles and fed on small pieces of ripe fruits. These advantages have been utilized to the full and the author believes that, as a result, some of the basic problems of heredity have been solved. In fact the opening statement in this book is: "That the fundamental aspects of heredity should have turned out to be so extraordinarily simple, supports us in the hope that Nature may, after all, be entirely approachable. Her much advertised inscrutability has once more been found to be an illusion due to our ignorance." The book deals with both genetics and cytology and the main thesis is the chromosome theory of heredity. According to this the chromosomes form the material basis of heredity. The various factors, upon which the manifestations of characters depend, are resident in the chromosomes, whence they influence the nature of the cells and of the organism which the cells collectively build up. The six principles of heredity are discussed in the light of our present knowledge of the chromosomal mechanism.

Due recognition is given the valuable work of Carothers on the mechanism of assortment and that of Wenrich on crossing-over and the linear order of the material of the chromosomes. The involved portions of the discussion will appeal more to the specialized student of this subject, but there is much of interest to the general scientific reader. Those interested in the study of genetics will look forward to reports of the work being done this year in California by Professor Morgan and his associates.

W. H. F. A.

THE NATURE OF ANIMAL LIGHT. By E. N. HARVEY, PH.D., Professor of Physiology, Princeton University. Pp. 182; 35 figures. Philadelphia and London: J. B. Lippincott Company, 1920.

ONE of the first questions asked the author when discussing the nature of animal light is whether it is likely ever to be used for commercial purposes. In spite of the negative answer to this inquiry there are other interesting points of view from which the subject will continue to be studied. The historic sketch of early observations of these phenomena, though short, is full of interest. Aristotle's name which is at the beginning of every science, appears also in this. In the days of "laudable pus," wound-infection by luminous bacteria, which caused the wounds to glow at night, was rather welcomed by surgeons. In the animal kingdom there are at least thirty-six orders known to produce light, and two groups among plants. The light is of the nature of luminescence, *i. e.*, its emission is stimulated by some other means than heat. After chapters on luminescence and incandescence, physical nature of animal light and structure of luminous organs, follow two chapters on the chemistry of light production. In these the properties of the three principal substances concerned in this phenomenon, luciferin, oxyluciferin and luciferase, are discussed at length and the author gives the results of his own studies. W. H. F. A.

DAS GESCHLECHTSLEBEN DER NATURVOELKER. By H. FEHLINGER. Pp. 93; 9 illustrations. Leipzig: Curt Kabitzsch, 1920.

THIS little paper-bound brochure is a monograph devoted to the consideration of the sexual life and customs of aboriginal people. The topics considered include the attitude of these people toward nakedness, prenuptial freedom and marital fidelity, courtship, marriage, childbirth and induction of abortion, the ignorance on the subject of generation, disfiguration of the genital organs,

sexual maturity and the post-sexual life. It is illustrated by means of some very interesting actual photographs of savage people, showing the lack of body covering prevalent in such tribes. The article is written in a very interesting style and the previous literature on the subject is freely quoted. It should be of interest to students of eugenics. F. B. B.

EXOPHTHALMIC GOITER AND ITS NON-SURGICAL TREATMENT. By ISRAEL BRAM, M.D., Instructor in Clinical Medicine, Jefferson Medical College, Philadelphia; Physician on Visiting Staff of Philadelphia General Hospital; Member of the Society for the Study of Internal Secretions, Etc. Pp. 438. St. Louis: C. V. Mosby Company, 1920.

COMING at a time when the surgical treatment of exophthalmic goiter seems to be on the defensive, any book on the non-surgical treatment of this disease is of noteworthy interest. Coming in a day when surgery claims so much and sensationally holds the therapeutic field, the author of this work is to be congratulated upon his daring to claim openly anything whatever for medical treatment. We believe that hyperthyroidism properly belongs in a majority of cases to non-surgical therapeutics, but we are rather disappointed that no stronger case against the scalpel has been made out by the writer's experience.

Eight case histories with their physical examinations are presented as being "illustrative of the potentiality for cure of exophthalmic goiter by non-surgical means." There are no records of laboratory work included in the histories, and nothing is said of metabolic studies. One of these cases was treated by mail and was never seen by the author.

In addition to these cases "selected at random" two chapters are devoted to the anatomy and physiology of the thyroid. Other chapters are given over to the pathology, pathogenesis, symptomatology, diagnosis, prognosis and non-surgical treatment of exophthalmic goiter. Some of the chapters are with few changes the author's reprints of articles published elsewhere in the literature. Such a chapter is the one on Shell Shock (?) in Soldiers.

The chapter on therapeutics is interesting, but offers no new ideas on treatment. Most of the suggestions have been used for a long time and are such as have yielded results for many men in some cases of toxic goiter. In other parts of the book much of the general literature on this endocrine dysfunction is utilized as a background, and in this way its non-surgical aspects are well supported.

The nature of endocrine disturbances *a priori* always leads to differences of opinion, theorization and questionable conclusions.

There seems to be no doubt in the author's mind that proper medical care of thyroid intoxication will yield 100 per cent. cures. We should be surprised to see some cases of exophthalmic goiter yield to any sort of therapeutic procedure.

We must, however, again congratulate the writer on calling attention to the fact that medical procedures in exophthalmic goiter are not without results if the patient is not too toxic and can economically devote enough time to the treatment. T. G. S.

MARINE HYGIENE AND SANITATION. By GILBERT E. BROOKE, M.A. (CANTAB.), L.R.C.P. (EDIN.), D.P.H., F.R.G.S., Chief Health Officer, Straits Settlements Medical Department, Port Health Officer, Singapore; Lecturer in Hygiene to Singapore Medical School; author of "Tropical Medicine, Hygiene and Parasitology," "Essentials of Sanitary Science," "Aids to Tropical Medicine," etc. First edition. Pp. 402; illustrated. New York: William Wood & Co., 1920.

THE author aimed to write a handy, practical manual of "sailing directions," and has succeeded. This book is the outgrowth of everyday experiences.

The introductory chapter on the ship's surgeon deals with the growth of the idea of using medical men on men-of-war and merchant ships, a practice dating back to about 1600.

The chapter on the structure of ships, with its glossary, is a necessary forerunner of the subjects of ventilation, fumigation and extermination of vermin. When one counts in the pages on this topic seven species of the rat family, at least fifteen species of fleas, several species of bed-bugs and eleven tribes of cockroaches, "all of which may be found on ships trading between Europe and the tropics," one has a more kindly feeling toward the executive officer of such old ex-commerce destroyers as the "De Kalb."

There is practical advice on the watering of the victualling of ships, on quarantine inspection, on ship-borne infections and how to handle them, and on sanitary inspection and disinfection of ships.

There are articles on port health officers, light-houses, light-ships, dietetic schedules, supply table lists, signal codes, etc.

The rulings of the Inter-Sanitary Convention, Paris, 1911-1912, concerning plague, cholera and yellow fever, appear in an appendix. One feels that this manual is a mine for the naval reservist of the medical corps, for those entering the medical service of the merchant marine, and also that it contains many practical suggestions and reference tables useful to the experienced sea-goer. J. E. T.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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A Study of the Correlation of the Basal Metabolism and Pulse-rate in Patients with Hyperthyroidism. — STURGIS and TOMPKINS (*Arch. Int. Med.*, 1920, xxvi, 467) report on 99 instances of hyperthyroidism, many of which were studied both before and after treatment of the condition. Four hundred and ninety-six basal metabolism determinations on 154 patients with hyperthyroidism demonstrated that in all but 16 per cent. the pulse-rate was above 90 per minute if the basal metabolism was +15 per cent. If the basal metabolism fell to normal the pulse-rate reached 90 per minute or below in 78 per cent. Only 5 patients with normal basal metabolism and without hyperthyroidism had a pulse-rate above 90 per minute. There is in general an interrelationship between the pulse-rate and metabolism when a group of individuals are considered: that is, an extreme degree of tachycardia suggests a greatly increased metabolism, while a slight tachycardia usually indicates a slight or moderate increase. The fact that a pulse-rate at complete rest below 90 per minute is seldom and below 80 per minute is rarely associated with an increase in metabolism is of practical importance in the recognition of the large group of nervous patients who have symptoms similar to those occurring in hyperthyroidism.

Observations upon Flutter and Fibrillation.—Part II, III, IV, by LEWIS, FEIL and STROUD (*Heart*, 1920, vii, 191). These papers by the author and his associates represent the results of experiments on dogs' hearts to determine the nature of auricular flutter and fibrillation. Direct graphic registration of the path of the excitation wave in flutter

of the dog's auricle was possible by means of electrodes placed at various points on the auricular wall. The details of the experiments, however, will not be given here. The excitation wave in auricular flutter courses around the orifice of the superior vena cava and surrounds a certain portion of the tissue lying on the inferior caval side of the superior orifice. The movement may be down or up the tenia terminalis. This central wave constitutes a continuous circus movement in a natural ring of muscle existing in the intact heart. "The presence of such a circulatory mechanism would explain long-continued flutter in the human subject and the high rate of auricular beating" and also "the close family resemblance of auricular flutter curves taken from different patients." When slight variations from the general path taken by the excitation wave occur the flutter is impure. "In flutter the excitation wave passes in equal times over equal stretches of auricular tissue; in impure flutter it does not appear to do so, and this is attributed to the establishment of local obstructions or actual barriers (block) which deflect the wave along new and sinuous paths. When this process involves not only the outlying regions of muscle, but also the path of the central wave, it is imagined that auricular fibrillations, as it is spoken of clinically, set in."

Mononuclear Leukocytosis in Reaction to Acute Infections (Infectious Mononucleosis).—SPRUNT and EVANS (*Johns Hopkins Hosp. Bull.*, 1920, xxxi, 410) report on six instances of mononuclear leukocytosis in response to an acute infection whose causal agent is unknown. All the patients were young adults. The symptoms were those of an acute infection associated with large, tender, cervical glands and usually with similar glands in axillæ and groins. The spleen was palpable in four instances. Fever was present for two to three weeks. The blood picture was strikingly similar in all the cases. There was a normal leukocyte count early in the disease followed by a leukocytosis of 13,000 to 20,000 per cubic millimeter. The increase was due chiefly to the presence of large numbers of large lymphocytes often in percentages from 30 to 60. The erythrocytes were normal. The prognosis is good. The authors believe the disease may be looked on as a "tentative" clinical entity. It can be differentiated from leukemia only by the subsequent course.

The Relationship of Smallpox and Alastrim.—COPEMAN (*Proc. Roy. Soc. Med.*, 1920, xiii, 237). The author describes an epidemic of alastrim in the counties in England in the summer of 1919, brought there by the captain of a boat from a Mediterranean port. The incubation period was from twelve to fourteen days. The onset was often abrupt, with headache, prostration, pain in the back and nausea. A chill was infrequent. The fever often was 103° or 104° F. The eruption appeared on the second or third day, followed quickly by disappearance of symptoms. One rachitic infant died. The eruption is characterized by the formation of papules, which soon become vesicular, scattered over the chest, abdomen and extremities, and usually later over the face. It rarely appears on the mucous membranes. The lesions often appear on the palms of the hands and the soles of the feet. They

tend to coalesce. The lesions are not umbilicated nor multilocular, and often do not become pustular. Pitting is uncommon. The differentiation from variola and varicella was often difficult. Vaccination against smallpox did not protect and patients who had recovered from the disease were successfully vaccinated against smallpox. The author describes epidemics of a similar disease in Cambridge (in 1903, 154 cases) and in Trinidad (in 1903, 4000 cases). He states that all these variola-like diseases should be controlled as though they were true variola.

Acute Respiratory Infections at the Boston City Hospital.—LOCKE, THOMAS, O'HARA (*Boston Med. and Surg. Jour.*, 1920, clxxxiii, 480). In this article the authors emphasize the importance of special pneumonia services and give some details of the plan of organization. Some of their statistics are of special interest. Thus in the early weeks of the epidemic of influenza the percentage of cases with pneumonia was low (27 per cent.), but reached 77 per cent. by the ninth week. The epidemic by that time was rapidly subsiding. The death-rate, however, was highest during the early weeks of the epidemic and lowest after the thirteenth week. Practically every death among influenza cases was due to pneumonia. Of the 740 influenza-pneumonias the mortality was 54.7 per cent. The examinations of sputum in influenza-pneumonia demonstrated the extreme rarity of Type I and II infection. As a rule, more than one organism was present, the most frequent combinations being pneumococcus Type IV and B. influenzae. *Lobar Pneumonia:* There were 447 cases of lobar pneumonia from February 3, 1919, to April 30, 1920, with 25.5 per cent. mortality. Of the total number 116 were Type I, 99 Type IV, 71 Type II and 49 Type III. Serum treatment of Type I cases, if employed before the seventh day, was of value. Empyema followed pneumonia in 66 instances. All were due to the pneumococcus following lobar pneumonia, while in cases of empyema occurring with bronchopneumonia none was caused by this organism. All of the latter except two were caused by streptococci. The mortality of empyema was 22.7 per cent.; 17 per cent. for lobar and 69 per cent. for bronchopneumonia cases.

SURGERY

UNDER THE CHARGE OF

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The Management of Fractures of the Femur.—MOORHEAD (*Surg., Gynec. and Obst.*, 1920, xxxi, 288) says that war fractures of the femur were the most difficult to manage, the most likely to cause fatalities,

the most productive of deformity. Early in the war the death-rate from these cases was 80 per cent. The treatment of fracture of the femur starts with first aid designed to place the limb at rest in traction in a Thomas splint, or in traction straps with weights attached. Ambulance surgeons and first aid men should be supplied with Thomas splints. The patient and not the fracture will demand attention in the feeble or diseased. Any method that does not combine reduction with early massage and motion fails to give maximum service. The former idea that deformity and disability are inevitable in femur fractures should be abandoned. Two attempts at reduction should be made before skeletal traction or open reduction is performed. For the non-displaced and reducible group, plaster of Paris (spica or molded) is an efficient form of splintage. In the irreducible group, described skeletal traction by transfixation offers a safe and efficient form of splintage. This fracture entitles the patient to a high grade of surgical care and exacts from the surgeon a degree of diligence and skill at least equal to that necessary in the management of many other major surgical problems. Fractures have been too much slighted by surgeons and for that reason the fracture field is being encroached upon by orthopedists, who by their training are better fitted for the after-care than for the initial care of this acute variety of traumatic surgery. There is a great need for standardization and uniformity in fracture work and in no group is this more necessary than in fractures of the femur.

Etiology, Pathology and Clinical Features of Benign Exostoses.—ELIOT (*Ann. Surg.*, 1920, lxxii, 228) says that nutritive disturbances and traumata have long been recognized as important factors in the etiology of exostosis. In the former type the exostosis which is frequently multiple disappears when the nutritive disturbance is corrected. Eliot thinks that subperiosteal hematomas are the starting-points for more or less actively growing exostoses. At times these cannot be differentiated from the classic pointed exostosis, the result of continued or repeated friction. Although as a class benign tumors of bone are of slow growth, the case reported by the author reached a length of two inches in thirteen months, although friction played no part in this unusual development.

The Radical Treatment of X-ray Burns.—DAVIS (*Ann. Surg.*, 1920, lxxii, 224) says that while some of the x-ray burns seen today are only of the first and second degrees, the vast majority under his care have been of the third degree. A peculiarity of the burn is that several weeks or months may elapse before the extent of the damage done becomes apparent. The burned area may be considerably hollowed out, the skin is hairless and atrophied, smooth, dry and shiny, with or without a blotchy brownish pigmentation. In the majority of cases telangiectases are present. The tissue is hard and board-like and its outline may be quite regular. There is usually an irregular shaped patch of tightly adherent necrotic tissue occupying the central portion of the ulcer. They heal slowly, if at all, and then break down. They are exquisitely tender. Davis does not think there is any greater tendency to malignant degeneration in chronic x-ray burns than in

any other ulcer, unless the ulceration follows the breaking down of a patch of keratosis. Recent x-ray burns of all degrees should be treated as ordinary burns, but unless there is a fairly prompt response to such treatment, it is a mistake to continue it. In third-degree burns the ulcer and surrounding area of induration should be excised with a wide margin, down to healthy tissue. After excision the defect should be grafted immediately if the base of the wound is of normal tissue, but if doubtful tissue is left, grafting should be deferred until granulations form. The type of graft used depends on the situation.

Sarcoma of the Clavicle.—CALEY (*Ann. Surg.*, 1920, lxxii, 231) reports 109 collected cases of sarcoma of the clavicle, fifteen of which were under the author's observation. The author thinks that malignant tumors of the clavicle are comparatively rare, only 16 cases having occurred in about 275 cases of sarcoma of the long bones. Sarcoma of the clavicle occurs more frequently in men than in women, probably because of the greater liability of the clavicle to injury in the sex. A clinical history of pain and localized swelling of the clavicle usually following recent injury, with rapid increase in size, supplemented by a fairly characteristic x-ray picture, will usually make an early diagnosis comparatively easy without the necessity of an exploratory operation. Local removal of the tumor or even a limited, partial resection should be avoided. The treatment of choice, while the tumor is in an operable stage, should be total excision of the clavicle as soon as the diagnosis is made. As soon as possible after operation, a course of systemic treatment with the mixed toxins of erysipelas and *Bacillus prodigiosus* should be begun and continued for a period of at least six months. When possible this should be supplemented with local or regional treatment with radium or x-rays. The mortality of total excision of the clavicle under modern technic is so small as to be practically disregarded and the functional use of the arm remains unimpaired.

Gall-bladder Disease.—JACOBSON (*Arch. Surg.*, 1920, i, 310) gives a statistical study of gall-bladder disease. Next to appendicitis, gall-bladder disease is the commonest intra-abdominal lesion. From 5.7 to 6 per cent. of patients coming to autopsy show gall-stones. Of 80,802 autopsies only 16 per cent. had symptoms referable to gall-stones. W. J. Mayo, in 1244 cases in which operation was performed for uterine myoma, found incidentally 7.2 per cent. of gall-stones, and Peterson, of Ann Arbor, found 12.5 per cent. in 1056 cases with gynecologic lesions. At the Peter Bent Brigham Hospital there have been 470 or 4.1 per cent. of the surgical admissions in six years admitted with a diagnosis of gall-bladder disease. Of these, 397 came to operation. Gall-bladder disease—cholecystitis and cholelithiasis—is a disease of middle age occurring with special frequency in women and closely associated with the increasing incidence of pregnancy. Many cases evidently originate in early age and persist with only vague indefinite symptoms until later in life. Gall-stones are due in all probability to a hematogenous infection, commonly streptococcal, of the gall-bladder and biliary passages and are associated with an

altered cholesterin-content of the blood. Common duct and pancreatic complication are of frequent occurrence in the long-persisting cases. There appears to be no special dilatation of the extrahepatic biliary passages in the slow obliteration of the gall-bladder through chronic infective processes with fibrosis. Recurrences are due mainly to overlooked or reformed stones, persistence of the original infection or to its extension as a chronic pancreatitis. Injury to the biliary passages during operation is due to the rather frequent abnormalities in the bloodvessels and biliary passages. Cholecystectomy is the operation of choice in cholecystitis and cholelithiasis whenever feasible. There is a marked beneficial effect in the long-continued drainage of the biliary passages in the complicated cases of cholecystitis and pancreatitis. There is no special detrimental effect of cholecystectomy on the body economy. There is an increasing mortality rate with the increase in the complications of disease. This is an argument for early diagnosis and operation.

Distribution of Adenomyomas Containing Uterine Mucosa.—CULLEN (*Arch. Surg.*, 1920, i, 215) reports 18 cases in which adenomyomas consisting of a matrix of unstriped muscle and fibrous tissue with typical uterine mucosa scattered throughout were found in the uterus, the rectovaginal septum, the tubes, round ligaments, utero-ovarian ligaments, uterosacral ligaments, sigmoid flexure, rectus muscle and umbilicus. Occasionally normal uterine mucosa are found in the ovary. Adenomyomas form one of the most interesting groups of tumors that have to be dealt with in the female pelvis. The cases are reported with complete histories and pathological reports and each case is well illustrated.

Intussusception Resulting from Benign Tumor of the Intestine.—WILLIS (*Surg., Gynec. and Obstet.*, 1920, xxx, 603) says that from the standpoint of the surgeon it is usually held that benign tumors of the small intestine are comparatively unimportant. King, in 1917, was able to find only 118 cases of benign intestinal tumors where the diagnosis was confirmed histologically. In the past ten years Willis has had one case of fibroma and two cases of adenoma of the small intestine. He reports these cases and concludes that the possibility exists that benign tumors of the small intestine are of more frequent occurrence than the number of cases reported from surgical clinics would lead one to suspect. In 4165 autopsies performed at the Boston City Hospital adenomata of the small intestine were encountered four times. We do not often see these tumors in the operating room except when they are the cause of an acute obstruction of the bowel.

Tuberculosis of the Breast.—HAMILTON (*Surg., Gynec. and Obst.*, 1920, xxx, 567) reports a case of tuberculosis of the mammary gland. The patient was forty-four years old. The patient's husband died of tuberculous laryngitis eight years ago. The patient had pulmonary tuberculosis five years ago, the sputum being positive. The history of the present illness was as follows: Injury to the right breast three

weeks before, after which it became tender and sore and a lump appeared. A radical breast operation was performed. In reviewing the literature, Hamilton finds Sir Astley Cooper, in 1829, reported the condition macroscopically, while Dunbar, in 1881, reported microscopic examinations of the breast. Only 180 cases have been reported to date. Deaver and McFarland classify tuberculosis of the breast as primary and secondary. The avenue of entrance of the tubercle bacilli may be through abrasions of the skin of the nipple or from other primary foci. Slight trauma has been the exciting cause in a large percentage of the cases. The prognosis of primary tuberculosis of the breast is good, but in secondary tuberculosis the prognosis depends upon the primary focus.

THERAPEUTICS

UNDER THE CHARGE OF

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The Digestion of the Tannin Compounds Used as Intestinal Astringents by Artificial Digestive Mixtures. Synthetic Drugs, III.—Owing to the too irritant properties of free tannic acid in the stomach, various compounds of tannic acid with proteins, organic esters of tannic acid, etc., have been proposed, which theoretically are presumed to be insoluble in and largely unchanged by gastric juice but to be decomposed by the intestinal secretions. LEECH (*Jour. Am. Med. Assn.*, 1920, lxxv, 1120) studied a number of these preparations to determine: (1) During a specified time the solubility of the respective compounds in water, hydrochloric acid solution, acid and pepsin solution, sodium bicarbonate and pancreatic extract solutions, and (2) the percentage decomposition at various intervals during the digestion. He arrives at the following conclusions: Only one type of the tannic acid compounds studied completely resists the action of the gastric juice and is broken down in the intestine according to theory, *i. e.*, the diacetyl tannic acid compound. "Acetannin Calco" (one specimen only studied) was satisfactory. "Tannigen" was fairly satisfactory in some instances. "Protan" and "Tannoform" were both readily soluble in sodium bicarbonate mediums. They are probably not broken up to a great extent in the intestine. "Albutannin Calco" and "Albutannin M. C. W." were not nearly so resistant to the acid-pepsin digestion as "Tannalbin" and "Tannin Albuminate Exsiccated" (Albutannin Merck). Neither of the two latter was sufficiently

resistant to the acid-pepsin medium but both liberated free tannic acid in the alkaline-pancreatic medium. With the exception of the (single) specimen of Acetannin, none of the products which were examined according to the methods described in this paper conformed strictly to the claims made for them.

The Use of Arsphenamin in Non-syphilitic Diseases.—From a study of the literature, REASONER and NICHOLS (*Jour. Am. Med. Assn.*, 1920, lxxv, 645) conclude that for practical therapeutic purposes the beneficial effects of arsphenamin and neo-arsphenamin are most apparent in a limited number of spirochetal diseases. They act as a specific in Vincent's angina, relapsing fever, yaws, gangosa and pulmonary spirochetosis (if given early) in man, and in equine influenza. A therapeutic effect is noted in rat-bite disease, in certain dental conditions and in fowl spirochetosis. Good results have been obtained in syphilitics with a number of non-syphilitic conditions which are influenced adversely by that disease. Their use has been recommended in conditions in which arsenic is indicated; in such cases the effect is alterative rather than specific and there is no special advantage over liquor potassii arsenitis. No apparent benefit has been found in such other spirochetal diseases as Weil's disease and yellow fever. There is a limited effect on certain protozoal diseases, such as malaria (tertian and quotidian), some of the trypanosomiasis and leishmaniasis. This effect may be non-specific. With the exception of anthrax and possibly glanders few favorable results are reported in bacterial diseases. Except in Vincent's angina, arsphenamin and neo-arsphenamin should be administered intravenously in medium-sized dosage. Two or three injections usually are sufficient, except in pulmonary spirochetosis which may require a series of injections. In diseases showing liver involvement, neo-arsphenamin has been recommended, as it is supposed to be less toxic than arsphenamin.

PEDIATRICS

UNDER THE CHARGE OF

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Further Progress in the Study of the Relative Efficiency of the Different Mercurial Preparations.—RAMSEY and GROEBNER (*Am. Jour. Dis. Children*, September, 1920) found that mercurial ointment, 50 per cent., is to be preferred to the less concentrated forms and need not be repeated more often than twice a week instead of daily. The quantity of mercury absorbed is much increased by friction. Calomel ointment is absorbed but less rapidly, and to a less extent than the mercurial preparation, and should, therefore, be given in greater concentration. The salicylate of mercury in oil should be given hypoder-

mically twice a week instead of once a week. Mercuric chloride, by hypodermic injection, although the dose is very small, continues to be eliminated for six or seven days. The fact that its use is frequently followed by the appearance of protein in the urine should exclude it from the treatment of syphilis in children. Calomel by mouth is absorbed in small amounts and continues to be eliminated for a considerable time, so that it would be sufficient to give it at intervals of several days, in order to avoid diarrhea. Gray powder is absorbed to a small degree and eliminated rather rapidly, so that large doses repeated daily would probably be needed to maintain mercury in the circulation.

A Study of Streptococci Obtained from the Mouth in Cases of Chorea.—FLOYD (*Jour. Med. Research*, May, 1920) reports as a result of experimental work in the production of endocarditis, acute articular rheumatism and chorea one or more members of the group of streptococci have been found to be the organisms producing pathologic results. Positive cultural results in clinical cases have mainly shown the streptococcus group. The clinical sequence of tonsillitis, articular rheumatism, with chorea or endocarditis, points to a localized lesion producing periodic systemic infection. Experimental work shows a much higher percentage of carriers of certain types of virulent streptococci in the substance of the tonsils and about the teeth in cases of chorea than occur in normal controls. The frequency with which virulent strains of streptococci are found in the mouth in cases of infection of the meninges, the joint surfaces and the endocardium suggests more than a casual relationship between their presence in the mouth, and systemic disease. He suggests that the teeth and tonsils are in all probability the two portals of entry into the body for streptococci in producing any of these clinically grouped diseases.

Spasmophilia and Vitamins.—VON MEYSENBURG (*Am. Jour. Dis. Children*, September, 1920) thought that in view of the similarity between beriberi in its early stages and active tetany, a deficiency in the diet of the antineuritic vitamine might play a role in the causation of spasmophilia. In both conditions the nervous system is involved, giving rise to such symptoms as hoarseness and laryngospasm. The end-results of the two conditions are, however, entirely different, beriberi being rapidly fatal if not treated and spasmophilia terminating in death. The studies of the author served only to rule out any possible relation between the heightened electrical irritability or the so-called spasmophilic reaction and any deficiency in the diet of the water-soluble vitamin. The infants studied in this group all received liberal allowances of orange-juice in their dietary, yet they showed the electric reactions characteristic of spasmophilia. This was all the more interesting because of the antineuritic content of orange-juice as shown by Osborne and Mendel and later by Byfield and Daniels. The very frequent association of spasmophilia and rickets, and the prominence which has been given to the fat-soluble vitamins in connection with rickets, serves only to add interest to the normal electric reactions obtained in those children whose diet contained a minimal quantity of this factor. The evidence of these cases shows that increased electric reaction is not dependent on a deficiency in the diet of the water-soluble vitamine or of the other two known food accessory factors.

Three Pertinent Questions on Maternal Feeding.—MULHERIN (*Jour. Am. Med. Assn.*, September 25, 1920), in answer to the query as to the advisability of immediate weaning in uncomplicated pregnancy, says that Nature does not intend the mother to nurse a baby at the breast and to furnish nourishment for one in the womb as well. He states that pregnancy itself does not generate toxins or cause them to be formed in the mother. It is the exception rather than the rule for toxemia to complicate pregnancy. It is true, however, that pregnancy as a rule, causes a diminution in the flow of the milk, and the quality is lowered especially of the fats. Because of the difficulty of changing directly from maternal feeding to cow's milk, both in the mother pregnant with another child and in the mother suffering from typhoid fever, he advocates complemental feeding. By complemental feeding he means an artificial feeding given the baby after it has nursed. This differs from supplemental feeding, which is an artificial feeding in place of a breast-feeding. In order to successfully practice complemental feeding a few points must be remembered: After the baby has nursed from the breasts they must be emptied by manual manipulation of finger-milking. In cases where the baby is too weak to suckle the milk must be expressed from the breast and fed by means of a spoon or dropper. He claims that supplemental feeding is wrong in both principle and practice, but that with complemental feeding, breast-feeding can be established, maintained and reinstituted.

The Superior Longitudinal Route.—MCKEE (*Therap. Gaz.*, September, 1920) points out that in the study of infantile disease blood is frequently needed for cultural or biochemic studies. In the past it was difficult to procure. Intravenous therapy in infants as in adults is coming more and more prominently into use. Because of the small superficial vessels in infants it has been difficult to follow this method. The superior longitudinal sinus is a relatively large vessel, very near the surface of the body. Its walls are resistant, it is not easily displaced and it does not occupy anomalous positions. It would seem, therefore, to be the ideal to enter when blood is needed for laboratory investigation or when intravenous medication is required. There is little danger in entering the vessel, but no one should puncture a baby's fontanelle without a due sense of responsibility and without a knowledge of the method and of surgical cleanliness. The scalp should be shaved, scrubbed and painted with iodine. All instruments must be sterilized and the operator should wear rubber gloves. Two assistants are needed, one to hold the head steady and slightly flexed and the other to manage the syringe, tube or transfusion apparatus. The Heimholz needle-holder holds the needle in position and at an angle of 25 degrees. The needle used is a No. 18 or 20 Brown-Smith.

Social and Medical Aspects of Childhood Delinquency.—BROWN (*Jour. Am. Med. Assn.*, October 9, 1920) examined 150 delinquent children of New York and found about one-third could be classified as nervous. They showed various symptoms of either mild or severe character constituting a neurosis. In drawing general conclusions from this survey a few of the most striking features must be indicated. From

a careful observation of delinquent children one cannot but feel that by proper management these conduct disorders might to a great extent be avoided. Usually the child has been misunderstood. Efforts are made to force the child to do something that he is entirely incapable of doing. He may be nervous, lack emotional control or intellectual ability to carry out the task. This is the material from which delinquents are made. Delinquency is often a minor affair at first, but under repeated maladjustments, undesirable habits are developed. Preventive treatment is the only way to manage childhood delinquency. Economic provisions aiming at preventive treatment of these children would not be difficult. Provision should be made for the prompt examination of all cases showing evidence of not getting along well. Special classes in school, and even special schools with vocational classes, would be better than truant schools. Small beginnings have already been made in certain places to accomplish this purpose..

A Note on Vitamines in Relation to Scurvy and Rickets.—DAVIDSON (*Med. Officer*, September 25, 1920) became medical superintendent of a county infant welfare center in 1917. At that time the scarcity of butter and milk was pronounced and mothers and infants showed signs of fat deficiency and insufficient food. Scurvy and rickets were seen in many babies. Those who were not breast-fed were being fed on condensed milk and patent foods. Realizing that this procedure would lead to more rickets and scurvy, the use of all condensed milk and patent foods was condemned. The following method was instituted: All bottle-fed infants were placed on a ration of dried milk plus fruit juice. They all improved up to two or three months, at which period they seemed to stand still. Evidently they lacked something in the diet necessary for growth. Dried milk procured from cows grazed in rough and rocky soil of the hilly country was substituted for that produced from milk of cows pastured in the fertile meadows of the lowlands, because the former was richer in fats and possibly in vitamins. The change was a marked success as the infants increased in weight and became more healthy in appearance. In addition to this red bone-marrow extracted from the rib bones of calves with the addition of a small amount of malt sugar was given. In addition to these things the children received a teaspoonful or two of orange, turnip or lemon-juice.

The Diagnosis and Treatment of Hydrocephalus Resulting from Stricture of the Aqueduct of Sylvius.—DANDY (*Surg., Gynec. and Obst.*, October, 1920) says that cicatricial stenosis of the aqueduct of Sylvius is the most frequent lesion in congenital hydrocephalus, occurring in about 50 per cent. of the cases, and it is also found in a large percentage of cases of hydrocephalus occurring in infancy and early childhood. It may occur, but rarely does so, in adult life. Hydrocephalus always follows occlusion of the aqueduct of Sylvius. The third and both lateral ventricles progressively dilate. The fourth ventricle, being posterior to the obstruction, does not enlarge. In the gross the occluded aqueduct appears to be replaced by a fibrous tissue band, which microscopically is neuroglia. Microscopic remnants of the aqueduct are usually but

not always found. The stenosis may occupy the entire length of the aqueduct or varying parts. It may even be only a thin transparent membrane. The stricture may be only partial. Strictures of the aqueduct can be diagnosed and accurately localized. The indigo-carmin test will indicate that a stricture is present. By ventriculography the obstruction can be definitely located. Spontaneous relief is not possible. Surgical attempts to drain the fluid from the third ventricle to the exterior of the brain have all proved futile. The openings invariably close and the fluid cannot absorb in the subdural space. He suggests a surgical procedure directed to the cause. A new aqueduct is constructed and a tube is left in place for two or three weeks. This has been done on two cases, both recovering from the operation. One died of pneumonia several weeks later, but the other seems well one year after the operation.

OBSTETRICS

UNDER THE CHARGE OF

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Treatment of the Severe Vomiting of Early Pregnancy.—LYNCH (*Jour. Am. Med. Assn.*, August 16, 1919) contributed a paper upon this subject at the meeting of the American Medical Association. He has examined the statistics of various countries to determine the frequency of this condition. Statistics seem to indicate that the severe vomiting of early pregnancy was less frequent in Germany than in America, England, France and Russia. In the writer's experience 58 per cent. of his private patients gave a history of nausea and vomiting in early pregnancy in 45 per cent. of his hospital cases. So far as serious cases are concerned, Carl Brown is credited with the statement that in 150,000 pregnancies he saw no fatal case. Similar statements were made by other German and Austrian obstetricians. The records of death from pernicious vomiting in France and England indicate a higher mortality. In 1914 Bondy reported only 21 cases of pernicious vomiting in 10,000 pregnancies in Breslau. He quotes similar statistics in two German clinics. In 2750 clinic cases at the University of California Hospital 14 were admitted for the treatment of pernicious vomiting of early pregnancy. The writer believes that in some way in these cases the maternal organism is sensitized to vomiting while in a state of pregnancy. He does not explain what is meant by this statement, nor does he mention the absorption of syncytium, which to many obstetricians is a rational explanation of this condition. Possibly these two causes may be related and frequently appear in common. In the pathology of the condition the changes in the liver are clearly recognized. Milder cases dying of some other condition show little more than the cloudy swelling of the parenchyma of the liver. All fatal cases, or nearly all fatal cases, show decided structural change varying from simple fatty

degeneration to acute yellow atrophy. In the most marked type there are degenerative changes about the central vein of the lobule tending toward its periphery. Clinically these cases have been divided into reflex, neurotic or toxemic. But the clinical classification should depend upon the pathology, and this would indicate that severe cases are toxic and that the toxemia gives its most evident manifestation in changes in the liver. The writer believes that it is problematic whether the pathological picture presented in the liver of those who die from serious vomiting of pregnancy represents the various stages of the same disease. While the writer believes that American obstetricians do wisely in promptly terminating pregnancy when medicinal treatment fails, yet he does not share the opinion of Tarnier and Boudin that the disease does not tend to recur in subsequent pregnancies. He has observed numerous cases in which after the first toxemia of pregnancy others have been complicated in the same way. Recognizing the importance of ammonia in the urine as indicating a pathological condition, the writer believes that this is influenced profoundly by the type of diet and by medication and by other factors. He does not consider ammonia as probably an index of the functions of the liver, but states that the fact remains that it is increased in the condition of acidosis and serves the purpose of saving alkali for the body. His observations have shown him that in more serious cases there is an increase in urinary ammonia. He believes it better to state that ammonia nitrogen in terms of absolute amounts, since without this control the ammonia coefficient may be misleading. The coefficient is a proportion of the total urinary nitrogen that presents as ammonia. If the absolute amount of ammonia remains stationary the coefficient will decrease with the increase of total nitrogen and will increase with the fall of total nitrogen. This has been shown by Folin in studying the variations seen in health. If the total nitrogen remains stationary and the ammonia increases in amount the ammonia coefficient increases, thus resembling the curve of increase of ammonia by weight. This condition he states is infrequently seen in the severe types of vomiting. These patients are put upon restricted diet and so the total nitrogen in the urine comes largely from the breaking down of body tissues. Early in starvation the loss of weight depends greatly upon loss of fats as the fatty acids are oxidized largely by the glycogen stored in the liver. It is natural to find variations in the partitions of the urinary nitrogen in fat and thin subjects dependent in turn upon the relative importance of carbohydrates stored in the body suitable for oxygenization of the resulting fatty acids. Undoubtedly the character of the food last taken may influence the condition. The writer has studied the acid of the blood in normal pregnancy and finds that there commonly exists in normal pregnancy an acidosis shown by the tension of the carbon dioxide of the blood, although the blood readings in the majority of his vomiting series fall within the same range as cases considered clinically as normal. In studying the urinary ammonia in early pregnancy the writer states that he has never seen a patient, as judged by clinical means, in danger of life in whose urine ammonia was in normal limits. The fact that high ammonia is occasionally seen in cases that do not give symptoms of marked toxicity does not impair the truth of the general statement, since the loss of fatty tissues, the glycogen content of the liver and

muscles, the character of the food retained, the type of medication employed all constitute factors that must be considered in a given case. It has been suggested that this increased ammonia is caused merely by the acidosis of starvation. While it is evident that cases of pernicious vomiting are starving, one cannot believe that starvation is responsible for the entire condition. The variations in anemia seen in pernicious vomiting of early pregnancy greatly exceed those found in cases of starvation. A starving patient after taking food has the ammonia fall very rapidly, and individuals subjected to experimental starvation are able to be up and about. On the contrary, patients in early pregnancy with pernicious nausea have been in bed for some time, and some of them have retained some food by mouth and have received glucose by the blood or by the rectum. The total nitrogen in a woman with the pernicious nausea of gestation often falls below that encountered in any case of starvation. We must admit the existence of acidosis in pregnancy, but the tension of the carbon dioxide in the blood in the cases of pernicious nausea does not exceed that of normal cases in which there is no pernicious nausea. The writer believes that the decision lies in the clinical behavior of the patient. After abortion the conditions often return to normal with the cure of the vomiting, while many others succeed in bringing about this result by proper treatment with the preservation of pregnancy. In the simple cases there is usually an excess of acid in the stomach. Patients are relieved temporarily by taking food and the mouth is acid when tested by litmus. Constipation is almost invariably present. The writer recognizes three periods in the day in which vomiting is liable to occur: (1) in the early morning; (2) late in the afternoon; (3) shortly before noon. Many patients show vomiting in all three. Motor neuroses are very common in these cases. The patient is usually worse in the morning because of the long fast during the night, although the stomach usually empties itself in a normal manner during the night, so that the matter vomited in the morning is chiefly acid mucus. Vomiting may also occur immediately after taking food. The nausea in the late afternoon very commonly follows a bad luncheon, while those patients whose usual breakfast is coffee and rolls often have a wave of nausea about 11 in the morning. Some of the most obstinate cases, however, occur in those in whom the acidity is less than normal. In the management of these cases the writer urges a careful study of the gastric secretions and of all matter ejected. He believes in the importance of nervous reflexes, and posterior displacements of the uterus should be corrected and the uterus held in normal position by pessaries, although the writer states that he has never seen relief follow such treatment alone. The care of the bowels is exceedingly important and may be a matter of much difficulty. But few drugs should be used. Rest, ventilation, hygiene and proper clothing are all important. That vomiting may be a nervous habit entirely is the belief of the writer. Hence the importance of trying to break the habit by selecting the type of food most easy to digest and difficult to vomit. Absolute rest and quiet are of the greatest importance. Hospital care is best and patients are usually relieved in about ten days. The writer's cases are put to bed and food and drink by mouth stopped until there has been no vomiting for twenty-four hours; the bowels are kept open by Bailey high colonic flushing; 40 to 60 grains of bromide are given by the bowel every four hours; 8 to 10 ounces of glucose and

soda are given by the rectum at fixed intervals. The patient should be assured that when the first meal is given she will be able to retain it, and she is strongly urged not to form the habit of vomiting. In selecting food fruits or sweets are to be avoided. The meal should be of solid food. While there is excess of acid a diet of proteins, limited fats and restricted carbohydrates is best. A deficiency of carbohydrates is supplied by the glucose given by the bowel, while the sodium bicarbonate neutralizes the acidosis. A diet of meats, fresh toasted bread and butter, a small amount of milk and cream is especially useful. Four meals of such food should be taken in twenty-four hours. Fluid may be withheld by mouth for many days and until the diet has been extended to include vegetables. Then the meals may be solid and fluid in alternation in small quantities and at frequent intervals. Usually broiled steak, roast beef and slightly cooked scraped beef are best, and must be used for several days. If this can be done the diet may be enlarged. When the case is of the subacid type it is more difficult to manage and the diet must be enlarged and fewer meats used. As the patient improves the bromides are reduced and soda and magnesia are given in capsules by mouth during digestion. The writer has found ingluvin of value in some cases. The writer is strongly convinced that food should be solid, frequent and in small quantities. Liquid foods he believes are very easily vomited. He believes that patients crave acid drinks, but that this craving can often be satisfied by a mouth wash containing acid. It is difficult to manage these patients without good nursing, and the nurse must strictly follow the physician's orders. If the case is of a fulminating type or if black vomit occurs pregnancy should be interrupted at once. Very often it is too late when these symptoms manifest themselves. The writer states that we do not know a safe limit for the urinary ammonia. There is a close parallel, he believes, between the ammonia excretion of pernicious nausea of pregnancy and that seen in diabetes. He has used Ringer's solution with excellent results, given alternately with the glucose-soda solution. He has tried injections of normal pregnant serum, but without result. Corpus luteum and epinephrin have been of no value. If the acidosis is not influenced by treatment and symptoms continue severe abortion is indicated. When marked acidosis is absent the prognosis is more favorable. In making the prognosis the study of the urinary ammonia is of value. The newer methods of Folin and Van Slyke can be carried out by hospital interns and titrations with formaldehyde solution are sufficiently accurate for clinical purposes and comparatively easy to carry out. The method of abortion is important because the anesthesia sometimes creates great danger. Chloroform should never be used in any case in which it would appear that the liver has used up most of its glycogen. Chloroform causes serious damage to the liver, already the seat of a pathological process. Ether produces acidosis and adds to the vomiting. Anesthesia with nitrous oxide and oxygen enough given to complete anesthesia are indicated. If the fetus cannot be removed with the dilatation obtained by the solid dilator, vaginal hysterotomy may be indicated, especially if the cervix is long and high. The lessened resistance of the patient to infection must not be forgotten. The use of bags and packing often aggravate the symptoms. The bladder should not be invaded if infection and pyelitis are readily developed.

GYNECOLOGY

UNDER THE CHARGE OF

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Conservatism in Pelvic Inflammatory Disease.—Based upon an experience with 120 patients upon whom he has performed wedge excision of the fundus uteri in the treatment of inflammatory disease, SCHMID (*Arch. f. Gyn.*, 1920, cxiii, 164) summarizes his views upon the treatment of pelvic inflammatory disease as carried out in the gynecologic clinic at Prag. In the acute stage, the cases are treated conservatively in order that the diffuse peritonitis may have a chance to localize and possibly completely disappear. In the chronic stage, simple conservative measures will, in three-fourths of the cases bring about complete restoration or at least sufficient improvement so that the patient may resume her usual occupation. Minor operations on the adnexa can then be performed, such as release of adhesions, removal of one tube or the adnexa of one side followed by salpingostomy on the other side if the remaining tube is healthy or shows only minor changes. In severe disease of both sides in which the retention of one ovary is precluded, and in women over forty years with moderate bilateral disease, a radical operation should be done by the abdominal route. In cases of bilateral inflammatory disease in which at least one ovary can be conserved, if the patient is in the child-bearing age, both tubes and the more seriously diseased ovary together with a wedge-shaped portion of the fundus uteri should be removed while the less diseased ovary or at least a portion of it should be allowed to remain. This fundus excision, which has recently been advocated in this country by Polak and known as the Bell-Beuttner operation, gives no higher mortality than the more conservative operations and has a lower mortality than the radical vaginal or abdominal operations. With proper technic it gives a subjective as well as objective satisfactory end-result in 83 per cent. of the cases with freedom from menopausal symptoms as well as the psychic shock of amenorrhea and with relief from pain and a complete restoration of the patient to her usual occupation.

Differential Diagnosis of Tumors by Means of Roentgen Ray.—By showing the manner in which neoplasms react to roentgen radiation, SEITZ and WINTZ (*Münch. Med. Wchnschr.*, 1920, lxvii, 653) believe that they have found a means of differentiating benign from malignant tumors. After roentgen radiation, if the tumor begins to show regression in a few days and has more or less completely disappeared after four or five weeks, it is probably a sarcoma. If, on the other hand, the regression

of the tumor after radiation first appears after three or four months and continues very slowly, consuming one to two years for complete disappearance, it is a myoma in all probability. The diminution in the size of the myoma is a secondary effect and is due to ovarian influence. The young cells of malignant tumors are much more sensitive to the roentgen rays than are the mature cells of benign neoplasms and thus roentgen-ray treatment often assists in making a differential diagnosis between benign and malignant tumors. For example, a lymphosarcoma regresses very quickly under radiation, while a tuberculous glandular swelling disappears very slowly. Similarly in the differential diagnosis between carcinoma and sarcoma the roentgen ray may be of assistance. Large ovarian and abdominal sarcomata regress quickly after radiation while carcinoma reacts very slowly unless a carcinoma dosage is given, which of course is much larger than the ordinary dosage.

Operation for Pruritus of Anus and Vulva.—The operative treatment proposed by ALLEN (*New Orleans Med. and Surg. Jour.*, 1920, lxxiii, 127) has in view the separation of the skin from the underlying tissue thus dividing all the nerves which reach the affected parts, rendering them anesthetic, and preventing the skin from immediately healing to the underlying tissues by packing, which is kept up until a firm bed of granulation has formed, which usually requires about one week, when the packing is discontinued and the skin allowed to fall back in place where it soon is again firmly united, leaving an anesthetic area which nearly equals the extent of the undermined area. This anesthetic area is not complained of but is usually a quite welcome change. It gradually diminishes in size with the return of normal sensation after a few months and has in Allen's experience not been followed by a return of the pruritus. The operation upon the anal region is the simpler. The area involved must first be accurately determined. It is usually quite symmetrical and uniform on both sides. A series of incisions are now made beginning at the anal margin and continued outward to about one-half inch beyond the affected area, which is rarely more than two inches. A series of these incisions are made about one inch apart at the peripheral extremity until the entire perineal region has been covered. These skin strips are now dissected up, preferably with a scalpel, except at their two ends which are left attached. In separating the skin from the subcutaneous tissues but a small margin of tissue is left attached to its under surface to insure a sufficient circulation to prevent sloughing. As the pruritic area rarely involves the mucous surfaces the incisions need not invade them, and in a few cases where the vaginal mucosa seemed to have been involved it cleared up with the relief of the external parts. The operation upon the vaginal outlet is performed in the same general way as upon the anal region and should need no special description. After dissecting up the skin flaps the space beneath is packed with iodoform gauze. Frequent sitz baths with a liberal supply of soap has always been insisted upon as an after-treatment. They keep the parts cleansed and are more effective and comfortable than irrigations. The packs may occasionally need changing but often remain the full time, about one week. After the packs are removed the parts quickly unite. The total disability is about two weeks.

Treatment of Inoperable Cancer with Selenium.—The attempt to eradicate malignant disease by injection into the blood stream is of recent origin. The pathogenesis of cancer is as yet unknown, but it has long been our hope to discover some preparation that would cause the destruction of the proliferating cells, whether this proliferation be the entire morbid process or merely the manifest termination of other hypothetical local changes. It having been observed, however, that cancerous tissue possesses the property of concentrating in itself the mercury given for the treatment of syphilis, experiments have been conducted to discover if other elements might not likewise be selected with this object in view; for it appeared possible that, if it were so, a protoplasmic poison might be given in doses which, though small enough not to injure the patient, might yet become sufficiently concentrated in the cancerous cells to effect their destruction. It was found that a large number of elements, chiefly metals and metalloids, showed this affinity in greater or less degree. WATSON-WILLIAMS (*British Jour. Surg.*, 1920, viii, 50) has been working along these lines with selenium. He states that the treatment appears to be suitable for two classes of patients. In inoperable cases, the results obtained compare favorably with any known method of attacking the growth by the blood stream, and are approximately equal to those of radiotherapy. The moderate focal reaction is in no way comparable to the local reaction from radium: the preparation appears to be considerably more active than copper. All malignant tissue is affected, however inaccessible. As a purely palliative treatment, the drying of ulcers and abolition of pain is a marked advantage. The injections have the minor advantage of low cost. As an adjunct to operative measures, including diathermy, the treatment may be applied to a variety of conditions. Where operative removal has not been as free as desirable, the possible outlying cells might be destroyed by injections. In patients having a course of injections, wounds in carcinomatous tissue have been observed to heal. Cases pronounced inoperable may give hope of becoming operable when sepsis and fixation have been diminished by this treatment. Possibly malignant processes might be held in check for a few weeks in patients who cannot arrange to submit to an operation at short notice: time is necessary before deciding as to the value of selenium in such cases. The effects following a course of injections are usually well marked. They are gradual in their appearance, and the improvement continues for some time after the injections have ceased. The first effect is noticed by the patient and is a local one, namely, diminution or disappearance of pain. In a favorable case there follows diminution in tenderness, cleansing of ulcerated surfaces, decrease of discharge, granulation, diminution in size and hardness of the tumor and secondary deposits, increased mobility of the part. In the general condition one may note improvement in anemia and cachexia, improved sleep and memory, increase in weight and strength, marked psychic improvement: this is due partly, no doubt, to the feeling that something is being done but is also largely attributable to relief from pain, sleeplessness and the intolerable discomfort of fetid discharges.

Combined X-ray and Radium Treatment of Uterine Carcinoma.—It has been the practise of SKINNER (*Amer. Jour. Roentgenology*, 1920, vii, 376) to accept no case for postoperative radiotherapy of a pelvic lesion unless deep x-ray intensive exposures through multiple portals of entry were used in an attempt to control the lymphatic metastasis at the same time that radium was applied to the cervix or uterus. He believes that the results obtained by roentgen therapy alone, before radium came into general use, warrant its continuation. By observation, he has acquired a criterion of prognosis in these cases, which is that cases which exhibit an early tanning of the skin offer the best prognosis. It is realized that tanning is a matter of skin type to a certain extent, and that it could be a matter of dosage and filtration. But when a uniform technic is used daily, he has constantly noted that the cases which tan quickly are doing better than those which do not tan. He is convinced that this is worthy of observation, as variation in technic did not produce tanning in the case that was losing the fight. It is generally acknowledged that the limits of radium activity producing reduction of cancer cells is 2 to 3 cm. which means that radium can have no action upon the pelvic lymphatics and other channels of metastatic progress unless there is an open operation which permits the planting of radium directly to the suspicious tissues or unless a large amount of radium is available to reproduce the effects of cross-fire roentgenization of these tissues. On the other hand, the limits of roentgen therapy are not measured by 2 or 3 cm., and the ability to cross-fire and thus accumulate x-ray tissue effects at any depth is simply a matter of careful and tedious technic. The question of the vulnerability of neoplastic tissue has been followed up in clinical and physiological observation. The cells are destroyed more readily in their lower state of development than in their more adult state. The aim of the postoperative radiations is not merely to destroy any cells which may have been left, but to prevent in the earliest stages the development of recurrences, and with this idea in mind the irradiations should be continued for a length of time at increasing intervals, sufficient to cover the period of probable recurrence.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Action of Benzol.—WEISKOTTEN, GIBBS, BOGGS and TEMPLETON (*Jour. Med. Res.*, 1920, xii, 425) report an interesting series of rabbit experiments on the action of benzol. The suggestion for this work was provided by the report of Selling (1910) of a series of cases of benzol poisoning occurring in girls in a factory where the rubber for soldering was held in solution in benzol. The predominating clinical features in these instances were purpura hemorrhagica, anemia and leukopenia.

Later in animal experimentation, Selling, and White and Gammon were unsuccessful in many attempts to produce anemia and leukopenia in well rabbits by the inhalation method *per se*, although Selling was able to obtain the desired result by the hypodermic injection of benzol in olive oil. In the present series, healthy rabbits were placed in a chamber containing vaporized benzol in concentrations comparable to that occurring in the factories. No accurate check on the amount of benzol was made although it was endeavored to maintain a maximal sublethal dosage. The average amount of benzol vaporized was 16.6 c.c. per hour. By meter it was found that 71.4 liters of air-benzol mixture were being pumped into the animal chamber every hour. Eleven animals were used. Six of the rabbits were placed in the chamber for ten hours daily while the remaining five were constantly immersed in benzol vapor excepting for a few minutes each morning when they were removed for purposes of weighing and blood analysis. The results were similar in both sets of animals. Within the chamber maximal sublethal dosage of the vaporized benzol was persisted in until the animals ceased to eat and were quite ill, at which time, if exposure was not complete, the concentration of the benzol vapor was diminished sufficiently to permit the recovery of the rabbits. Of the eleven animals only four survived the tests and autopsies performed upon the dead rabbits showed edema of the lungs, pulmonary and gastro-intestinal hemorrhages and ulcerations of the gastric mucosa to be the outstanding features. It is noted that in the leukocyte curves and erythrocyte curves, a permanent lower level was struck following the subjection of the rabbits to the benzol vapor. In the case of the leukocytes this was reached about the sixth day after exposure while in that of the erythrocytes it was attained from the sixth to the sixteenth days. All animals demonstrated a definite weight loss which continued throughout the period of exposure. The authors through their careful investigations, demonstrated conclusively that exposure of rabbits to benzol vapor with maximal sublethal dosage causes leukopenia, hemorrhages, weight loss and anemia, and that in the leukopenia the percentage and absolute decrease is greater in the small mononuclear cells than in the polynuclear amphophiles. It is observed, in addition, that after the discontinuance of exposure to benzol vapor the leukocyte curve gradually rises to a permanent general level which, however, is much lower than the normal permanent level prior to exposure and that the failure to return to normal is due to the inability of the small mononuclear curve to return to its preëxisting state.

Effect of Intrabronchial Insufflation of Acid.—The resemblance between the lesions of influenzal pneumonia and those produced by the inhalation of irritating gases suggested to WINTERNITZ, SMITH and McNAMARA (*Jour. Exper. Med.*, 1920, xxxii, 199) a series of experiments which might assist in the interpretation of the characteristic influenzal lesions. Inasmuch as the weight of evidence indicates that the lesions which these gases produce depend on the halogen radical and that the decomposition of these gases is associated with the formation of hydrochloric acid, this reagent was introduced by intrabronchial insufflation into rabbits in dilutions varying from 0.1 to 1.0 per cent. dilution. It was found that the acid so administered caused an immediate and

extreme damage of lung tissue. Within certain limits the degree and extent of injury varied according to the concentration of the acid. With greater concentrations death occurred almost immediately, while with weaker solutions the results, grossly and histologically, resembled those noted after influenzal pneumonia and gas poisoning, being associated with intense edema and congestion of the lung with hemorrhage, dilatation of the alveolar ducts and bronchioles, hyaline necrosis of the epithelium of these structures, and lobular, pseudolobular, and lobar types of consolidation which were mostly serofibrinous but sometimes hemorrhagic or purulent.

Histological Changes of the Different Types of Carcinoma after Exposure to Radium Rays.—ALTER (*Jour. Med. Res.*, 1920, xli, 439) presents a review of comparative studies of the effect of radiation upon the various carcinomata and incidentally gives an estimation of the worth and the limitation of radium in the clinical field. Broadly, the writer groups the malignant tumors into a combined histological and anatomical classification and by microscopical description demonstrates the variations in reaction to radium by the different types of growth. Beginning with the basal cells, cancers of skin, the less specialized and most embryonal types, wherein radium produces a complete destruction and absorption of the tumor cells, the author gradually ascends the scale to the tumors derived from highly specialized, particularly functioning epithelium in which the radiation results in the extreme opposite, namely that of hastened functional activity or specialization. However, it is not inferred that the process in the latter series is uninterrupted for here, too, much of the undifferentiated tissue succumbs and is absorbed. Apparently each type of carcinoma has a particular mode of response to radiation and this reaction is determined to a great degree by the physiologic function or grade of specialization of the particular type of cell in the body. So it is that the embryonal basal cell tumor with no especially differentiated characters "melts away" before radium, while just a step higher the prickle cell cancer though partially destroyed, is hastened toward its particular form of differentiation. The adenocarcinomata tend to approach the normal character of the tissue and manifest hypertrophied function under the stimulus of radiation. The inference is clearly drawn that the least differentiated types of tumors are more prone to destruction by radium and therefore this mode of treatment has its maximum value in such cases. The author states that all tumors undergo a period of latency following radiation subsequent to which a primary swelling of the cells occurs. From this point, in the basal cell types, a progressive destructive process ensues, while in the differentiated types the specialized functional activities are hastened. It is clearly shown that the response to radiation is no more than an expression of transformation of energy. The energy required in the fulfilment of the hastened functional activities can be derived only at the expense of one other source, namely, from the capacity for multiplication and growth. This is corroborated by the infrequent finding of mitotic figures in the nuclei of cells subjected to radium therapy. Hence the retardation in growth of tumors following radiation is easily explained. The degree of effect of radium rays on tumor

cells, the author maintains, is proportionate to the amount of rays absorbed and that different nuclei and protoplasm absorb different amounts. The quantity absorbed is dependent upon intracellular physicochemical or chemical conditions which the writer feels would furnish an interesting field for study.

HYGIENE AND PUBLIC HEALTH

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Notes on Typhus.—WOLBACH, TODD and PALFREY (*Internat. Jour. Public Health*, September, 1920, No. 2, i) were members of the Typhus Research Commission of the League of Red Cross Societies to Poland. They did their work last winter in Warsaw. These investigators planned a series of experiments with the purpose of determining the nature and specificity of microorganisms acquired by lice fed on typhus fever patients. Thirteen unsuccessful attempts were made to cultivate the organism described by Plotz. They find that the distinctive pathology of typhus fever is microscopic. The disease is characterized by lesions in the smaller bloodvessels. The vessels of the skin and the smaller vessels of the central nervous system are most often affected. The earliest lesion noted is a reaction of the endothelium, which proliferates, followed by degeneration and necrosis. In larger vessels these processes lead to a formation of thrombi; in smaller vessels there is sometimes a destruction of continuity followed by an extravasation of blood. This occurs most often in the capillaries of the skin and brain. Occluding thrombi of the larger arteries and veins of the skin frequently occur, but mural thrombi are constant. These changes are so characteristic that a diagnosis of typhus fever can be made from the skin excised during life; in only one other disease, Rocky Mountain spotted fever, do similar lesions occur. In the endothelial cells of vessels presenting lesions a microorganism has been found. This is similar in appearance to that described in Rocky Mountain spotted fever (Wolbach: *Jour. Med. Res.*, November, 1919, p. 197) and in the typhus fever of Mexico (Wolbach and Todd: *Jour. Inf. Dis.*, July, 1915, p. 1). The organism has been seen in 13 instances in skin excised from patients during life and in 22 instances in tissues obtained at autopsy. The most easily demonstrable form of the organism occurs in clumps; the individual organisms are pairs of slightly elongated bodies with tapering ends. They are surrounded by an unstained area. The length of a paired

organism is from 1 to 1.5 microns. Isolated pairs and groups of several pairs are found with considerable frequency in swollen endothelial cells both in relation to thrombi and remote from lesions; they are found both in tissues taken during life and in material obtained shortly after death. A second form of the organism, occurring much less frequently, is a minute paired granule which fills endothelial cells while they are still *in situ*. In skin excised during life and in tissues obtained at autopsy, peculiar swollen and vacuolated endothelial cells are seen; in the authors' experience, they occur only in typhus. In them are numerous granules, which often completely fill the cell. The granules are very small; they are at the limit of visibility. They are being studied as a possible third form of the parasite. All forms of the organism stain blue. The larger paired forms are deeply colored; the other forms retain the stain less densely. Typhus was transmitted to guinea-pigs by the inoculation of infected lice. The disease runs the recognized course in infected animals. Characteristic lesions occur in the brain. The testes and epididymis often show an occasional vessel with lesions of the intima, thrombi and perivascular reaction quite similar to those observed in patients. The larger forms of the organism as seen in man have already been found in the lesions of cerebral vessels in the guinea-pig. Great pains were first taken to be sure that the stock lice used in the experiments were uninfected. It was found that the organisms were acquired by these lice when fed upon cases of typhus fever during the first ten days of the disease. The organisms are consistent in their characteristics with those described by da Rocha Lima as *Rickettsia prowazeki* (Da Rocha Lima: *Deutsch. med. Wchnschr.*, July 3, 1919, p. 732). They are exceedingly pleomorphic. They vary in form from a minute, paired body to a bacilliform organism measuring several microns in length; both the minute and the bacillary forms occur in chains; the chains of bacilliform organisms often measure more than 15 microns in length. The organisms may be present in infected lice in extraordinary numbers. Every epithelial cell lining a louse's gut may be enormously distended by myriads of organisms, and through the bursting of the cells many organisms may be set free into the lumen of the gut. The distended cells of a heavily infected louse can be easily seen with a low magnification (objective 16 mm.) or even unstained with a dissecting microscope. All forms of the organism may be present in the distended cells of a heavily infected midgut; but the small forms occur most frequently and, as a rule, occur in cells that are most distended. The authors have formed the impression that the bacillary phase occurs early in the infection of a cell and that the minute form of the organism is characteristic of an advanced cell infection. As a rule, all organisms, whether intracellular or free in the lumen of the alimentary tract, stain blue; occasionally, organisms free in the gut are colored red, possibly because of variations in technic. The authors state in conclusion that in lice fed upon typhus patients under conditions determined to be favorable a peculiar, pleomorphic microorganism is constantly present. This microorganism is that named by da Rocha Lima *Rickettsia prowazeki*. In the vascular lesions of man and experimental animals infected with typhus a minute microorganism has been demonstrated. In morphology and staining reactions it is consistent with *Rickettsia prowazeki* in at least two of the forms in which it is seen constantly in lice.

Influence of Smallpox and Vaccination on Pulmonary Tuberculosis.—HOWK and LAWSON (*Am. Rev. Tuberc.*, September, 1920, No. 7, iv, 490) record an epidemic of smallpox occurring in the Metropolitan Life Insurance Company Sanatorium in the autumn of 1914. Time was purposely allowed to intervene between the epidemic and the writing of a formal record of it in order that the observations might show, not alone the immediate effects, but some of the remote influences of smallpox on pulmonary tuberculosis as well. There have been few similar experiences reported, nor is more than brief mention made in any of the writings on exanthematous diseases of the possible or probable effect that smallpox may have on clinical tuberculosis, although the literature is quite replete with reports of certain other concurrent complications of pulmonary tuberculosis. There were 7 cases of pulmonary tuberculosis which contracted smallpox, all of which recovered. In 1 case there was a moderately severe bronchitis following the onset of smallpox. There was no development of pneumonia in any case. The smallpox was of a mild form in 6 cases, severe in one, and its course was apparently unaffected by the presence of tuberculosis. The one outstanding feature of the tuberculosis following smallpox was the marked diminution of expectoration in two advanced, active cases. The effect was more striking than anything witnessed in tuberculosis, except the reduction following artificial pneumothorax. In 1 case there has never been any return of sputum or bacilli, although the patient had extensive basal lesions. In the other the sputum and bacilli were absent for four months. The authors conclude that smallpox, occurring in patients with pulmonary tuberculosis, runs a course not noticeably different from that encountered in well people. The symptomatology, appearances of exanthem, and duration of the smallpox are not influenced by the presence of tuberculosis. In early, inactive cases of tuberculosis with favorable prognosis there is no apparent interruption of recovery when complicated by smallpox. In 1 active advanced case there was a disappearance of sputum and bacilli after smallpox, lasting for four months. In one very very active and advanced case there was a permanent disappearance of sputum and bacilli immediately after the smallpox. The disease was progressive up to the time of smallpox and retrogressive thereafter. The 7 recovered from smallpox and 6 are alive and well at present. The presence of tuberculosis does not affect the normal course of vaccinia. Tuberculosis in any stage or any degree of activity was not affected by vaccination, either favorably or unfavorably.

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ORIGINAL ARTICLES.

ACUTE PSYCHOSES ARISING DURING THE COURSE OF
HEART DISEASE.¹

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ACUTE mental disturbances sometimes appear during the course of heart disease with such startling suddenness as to disconcert the attending physician and to prove a severe shock to the patient's family. The majority of text-books are silent on this subject, yet the condition is one upon which both from the point of view of etiology and of prognosis much light is needed. Dr. Head, in 1901, in a masterly article,² called attention to the mental changes accompanying visceral disease, including heart affections; he concerned himself, however, chiefly with hallucinations of sight, sound and smell, and states of mild depression or exaltation, which he analyzed with very keen insight. In keeping with the opinion of the day in which he wrote, he speaks of aortic valve disease, mitral regurgitation and mitral stenosis, but does not mention that great group of cardiac affections in which valvular lesions play a subordinate or negligible part.

It is of course well known that cardiac patients often are depressed and irritable, particularly after decompensation has been established, and sleep, digestion and respiration are in consequence disturbed. The particular state of mind is closely related to the

¹ Read before the Association of American Physicians, Atlantic City, N. J., May 4, 1920.

² Brain, 1901, 24, 345.

patient's temperamental make-up and to his philosophy of life. I once had under my care a woman, aged about forty years, with the most hopeless cardiac break, with dropsy, serous effusions, large liver, cyanosis, insomnia and orthopnea, who until her death maintained a perfect sweetness of disposition and a hopefulness of spirit that was greater than any *spes phthisica* that I have ever witnessed. On the other hand, I have seen patients who when decompensation was far advanced, by their fretfulness and their unreasonable demands, made life miserable for family, doctor and nurse. But while such a mental condition is abnormal it cannot be called a true psychosis. Nor shall I consider among the cardiac psychoses the delirium of acute and subacute septic endocarditis, since that is dependent more upon the infectious toxemia than upon the heart disease as such.

The manifestations of true psychoses are quite varied. Among the more important types are the following:

1. **Hallucinations** of sight and sound, more rarely of smell. These were found by Head³ to be most frequent in aortic disease. The auditory hallucinations consist chiefly of rhythmic sounds like the tolling of bells or of knocking; the visual usually take the form of the face of a man or woman with dimly outlined body standing at the foot of the bed or stalking slowly across the room. The patients as a rule recognize the hallucinatory character of the sound or vision and are disinclined to speak of it until the physician has gained their confidence. Hirschfelder⁴ states that a number of patients admitted having hallucinations after he had assured them that visual hallucinations were not uncommon in their disease and were merely to be regarded as troublesome but not as significant features. All who gave positive answers accurately described the visual hallucination as detailed above.

The hallucinations are to be looked upon as misinterpreted sensations caused either by anemia or by venous stasis of definite brain centers—those connected with sight or hearing—or by circulatory or trophic disturbances in the corresponding peripheral end-organs. They are usually of a transitory character and do not affect the prognosis in any definite manner.

2. The most common cardiac psychosis is a state of *confusion*, in some cases present only as the patient awakens from sleep or is about to go to sleep; in others it is a more or less constant symptom. The patient confuses his surroundings, is disorientated as to time but may become rational when his attention is sufficiently aroused. This mild type of psychosis is common in myocardial cases with auricular fibrillation with or without decompensation. The less the natural sleep the greater the confusion.

³ Loc. cit.

⁴ Diseases of the Heart and Aorta, Philadelphia, 1918, p. 229.

3. In some cases, especially in elderly persons suffering with fibroid myocarditis, the mental state is one of *excitation with decided disorientation*. Such a type is illustrated by the following case:

Mrs. F. H. W., aged seventy years, with cardiac hypertrophy and hypertension, dyspnea on exertion and a little edema of the lower limbs, suddenly began to exhibit a state of mental confusion and excitation which was most marked when she awakened from sleep. She would stare excitedly about the room, talk incoherently and try to get out of bed. When engaged in conversation, she answered most questions pertaining to herself quite well, but to those dealing with the day's events or with familiar contemporary history, she gave confused and inappropriate answers. There was no evidence of motor weakness or paralysis; indeed, she seemed surprisingly strong. The urine contained a faint trace of albumin, no casts, no blood, but a very large quantity of urates; its specific gravity ranged from 1012 to 1022.

The prognosis in such cases is not good, death usually following within a few weeks after the onset of the psychosis. The patient may, however, clear up if the myocardial degeneration has not gone too far and if no complications ensue. In the case just mentioned a pneumonia supervened.

In some cases the state of excitement alternates with one of complete apathy and silence—the patient may sit up promptly when the doctor approaches and may stare directly at him, but answers no questions and does not betray by any sign that he understands what is said to him. Such taciturn myocardial patients have to be watched as they may suddenly become agitated, get out of bed, and make powerful muscular efforts that may end in collapse.

4. Perhaps the most interesting, certainly the most startling disturbance arising in diseases of the heart is *acute mania* which may appear with the suddenness of an apoplexy and for a time defy all efforts at control. I have seen it appear under two conditions: in acute pericarditis and in advanced decompensation of myocardial origin. Its occurrence in pericarditis was pointed out long ago by Da Costa. The late F. A. Packard was the first to bring it to my attention when I was his intern in the Philadelphia General Hospital. We had in our ward a woman, Louisa Wilbur, who had an acute fibrinous pericarditis, the cause of which I do not remember. One day without warning she suddenly became wild and maniacal and had to be restrained. She remained in her state of mania until death. This experience impressed upon me the importance of examining for pericarditis all cases of sudden wild delirium or mania.

Mania in the course of myocardial disease is illustrated by the following case: W. M. R., a physician, aged about fifty years, was brought to my office in June, 1914, in a state of extreme shortness of breath and collapse, which had come on while he was cranking a refractory motor car. Examination showed total arrhythmia, an

enlarged heart, enlarged liver but no edema of the extremities. Under rest and digitalis the patient improved; the auricular fibrillation, however, was very slow in subsiding. Although he never regained his full strength, he was able to do a little practice until the spring of 1915; then, despite treatment, he began to lose compensation rapidly. At the beginning of June he suddenly started one day to "act like a crazy man," as his wife expressed it. For six consecutive hours he raced around his library table, throwing his hands wildly about and exclaiming: "I am a thief; no I am not. You are a thief; no you are not. I am a liar; no I am not. You are a liar; no you are not." These phrases he repeated over and over without stopping as fast as he could talk for six solid hours. It was only after Dr. H. MacVeigh Brown, with whom I was seeing him, had given three large hypodermic injections of morphin that the man quieted down. For nearly a week, however, he remained in a state of great physical agitation. He talked incessantly, mostly in a facetious vein, but without much coherence. Throughout that time he slept neither night nor day. It was a marvel to all of us how his heart stood the strain. Toward the end of this period another strange thing happened—the urine, which had been very scanty, became greatly augmented, the dropsy disappeared, and the man was able to lie down flat, which he had not done for a long time. He never regained his mind completely and died in stupor six days after the termination of the maniacal episode.

5. **Delusional States.** When delusions occur they usually take a persecutory form and render the patient most unhappy. While mania and mental confusion are not confined to any particular type of heart disease, I have seen delusions of persecution so far only in connection with lesions of the aortic valve. One of the cases was that of a young baker in my wards at the Philadelphia General Hospital, who had aortic stenosis of rheumatic origin. He thought he was being poisoned with gas by enemies in his shop. Under rest the delusion disappeared in a short time.

6. During attacks of Cheyne-Stokes breathing—a common symptom in cardiac disease—there is at times in the dyspneic period a state of mental excitement or delirium which subsides during the apneic period. The seizures of Adams-Stokes disease, which so closely resemble petit-mal, should also be mentioned here.

In considering *the causes of the cardiogenic psychoses* a number of possibilities suggest themselves:

1. The connection may be an accidental one. In an individual of psychopathic make-up the taint may at any time break forth quite independently of the existence of heart disease, although the latter would favor it by impairing the circulation. In asylums for the insane, cases in which the psychopathy is associated with disease of the heart are numerous. These chronic psychiatric cases do not, however, belong here, as this paper concerns itself only with acute manifestations.

2. A probable factor, in some cases at least, is disease of the kidneys, a frequent concomitant of disorders of the circulation. Uremia by itself is quite capable of producing psychoses, either of the maniacal or of the melancholic type. However, I do not believe that the passive congestion of the kidneys in decompensation of the heart, although often considered a true nephritis, is capable of producing a uremic state. As an accessory factor, it cannot be ignored.

3. I have sometimes thought that acidosis may play a part in the production of mental symptoms in cardiac disease. One often finds when the circulation is failing that the urine becomes intensely acid and throws down a heavy pinkish sediment of urates. This is such a constant phenomenon that I look upon it as possessing diagnostic value. It occurs in secondary renal congestion; not in primary nephritis. A study of the subject of acidosis in diseases of the circulation—the blood carbon dioxide, the hydrogen ion concentration, the ketones and other acid bodies—may, in the future, yield valuable information.

4. That drugs and poisons may be a factor is a natural assumption. An amount of alcohol that in otherwise healthy persons might not do any recognizable harm, may in a patient with disordered circulation lead to a psychosis. Some older writers have held digitalis responsible for maniacal and other acute psychopathic outbreaks. Duroziez⁵ reported a number of cases of delirium and coma, which he attributed to digitalis medication. H. O. Hall⁶ also called attention to delirium and hallucinations during the course of the administration of digitalis. In one case cited by him (p. 490), it would certainly seem as if digitalis had been responsible for a condition of mental depression bordering on melancholia. Babcock (quoted by Hall) noted in two patients a peculiar mental and emotional state that disappeared after the use of digitalis was discontinued. In the one case, that of a woman, with mitral stenosis, the mental disturbance took the form of a sullen moroseness with taciturnity; while the other patient, a man with aortic insufficiency, manifested a mild delirium of a harmless kind.

At the present moment I have under observation a woman with auricular fibrillation, who, after about the third or fourth day, became confused and talkative. She did not seem to know where she was, although on the occasion of my visits she would answer questions rationally. She herself said, both to the nurse and to me, that she thought the dark medicine did not agree with her. The dark medicine was tincture of digitalis, with a very small amount of tincture of belladonna. I thought that she might have a prejudice, so I substituted digipuratum for the tincture of digitalis. But she also objects to that, and I am strongly inclined to stop the administration of digitalis altogether.⁷

⁵ Gaz. hebdom., 1874, xi, 780.

⁶ Am. Med., 1901, i, 598; Ibid., 1905, ix, p. 489.

⁷ This was done but the psychosis continued, so that it is not likely that digitalis had anything to do with it.

While digitalis may in rare instances exert a direct action upon the brain, it is possible that in some cases when overdoses are given, it may, by disturbing the cardiac rhythm through its action on the conducting mechanism, still further impair an already inadequate circulation. On the whole, however, considering the universal use of the drug and the carelessness in dosage, one would expect that if digitalis could cause psychoses they would be much more frequent.

5. Several years ago I had the following experience: Mr. H. B. B., a man in the late fifties, was suffering with cardiovascular disease, with extreme dropsy. I tried digitalis and all other well-known diuretics without result. About that time agurin appeared on the market. I prescribed it and was amazed to find the urine output increased to an enormous degree, with a coincident rapid disappearance of serous effusions and of every trace of dropsy. During the time that the patient was putting out huge quantities of urine (in one day more than 200 ounces), he developed a delirious, incoherent state, which lasted several days and proved most distressing to his devoted family. I attributed it to a swamping of the system with the toxic material that had been held in solution in the dropsical fluid, and which, in order to reach the kidneys, had to return to the general circulation.

6. In cases in which the foregoing factors are lacking, in which the cardiac patient, without neuropathic taint, nephritis, acidosis or exogenous intoxication, develops an acute psychosis, we may assume that it is due to some direct disturbance of the cerebral circulation, affecting the higher centers. At times there is probably syphilitic disease of the vessels, but that is not a prerequisite. Dana's hypothesis⁸ concerning the part played by the neuronie synapses may help us to understand why, in disturbances of the circulation, alterations may occur in the psyche. Nevertheless, it is still a far cry from hypofunction of the synapses to an understanding of mental exaltation or depression, of hallucinations or of confusional states.

Not much need be said about treatment, which will vary with the type of disturbance found. Maniacal patients often do not respond to morphin or any of its congeners. I have obtained better results with chloral, which I believe to be not so depressive to the heart as it is usually considered.

As regards diagnosis, it is always necessary to bear in mind that acute mania or melancholia may be symptomatic of visceral disease, in particular, of disease of the heart, and that patients so affected are not of necessity subjects for the asylum. The prognosis is governed by the state of the circulation—if the patient's heart holds out his psychosis will disappear.

⁸ Jour. Am. Med. Assn., April 24, 1920.

WHOOPING-COUGH CONTRACTED AT THE TIME OF BIRTH, WITH REPORT OF TWO CASES.

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WHOOPING-COUGH during the first month of infancy is sufficiently rare that the two cases reported below, in which exposure occurred at the time of birth, are of considerable interest. The infection in each of these cases was from the obstetric nurse, who was in the first week of her attack of whooping-cough. Her cough was not of sufficient severity that she considered it necessary to report it to the obstetrician. In the first case reported she assisted, at the time of labor, the regular nurse for twenty-four hours, and then went to the second case, this baby being born three days later. Although her cough grew steadily worse she did not suspect that it was due to whooping-cough. It should be a golden rule that a nurse who has a cough should not take an obstetric case. I believe, too, that pertussis in adults is often unrecognized, and this is accountable in many cases for the spread of the disease. In one year in three different families, I saw six cases of pertussis contracted from nurses who had coughs, which they thought were due to "ordinary colds." The prevalent idea among the laity, and sometimes among physicians and nurses, that adults seldom contract whooping-cough is responsible for lack of quarantine.

The following are the two cases I wish to report:

CASE I.—Female, of healthy parents, was born May 28, 1914. The birth was two weeks premature and the weight of the baby was five pounds ten ounces. During the first three days the child lost six ounces, but these were regained by the end of the first week. A steady gain of one ounce a day was recorded until the tenth day, when the infant began to cough. On the eleventh and twelfth days the cough increased in severity, so that it interfered greatly with nursing, and the food was regurgitated. On the fourteenth day after birth the infant began to whoop, the paroxysms steadily increasing in number and severity, so that on the sixteenth day they numbered twenty-two. On the seventeenth day there were twenty-eight, on the eighteenth thirty, on the nineteenth thirty-eight. During the paroxysms the baby became deeply cyanosed and at times it was with great difficulty that breathing was again established. On the morning of the twenty-first day the infant became stuporous and within a few hours sank into coma; the fontanelle became tense and there was a paresis of one side of the face. The breathing assumed the Cheyne-Stokes type, with periods of apnea

lasting forty seconds. The coma deepened and death occurred that evening. No autopsy was permitted, but the cause of death was evidently a cerebral hemorrhage.

CASE II.—Female infant was born June 3, 1914, at full term, weight eight pounds fourteen ounces. The obstetric nurse in attendance had assisted as second nurse in the case of the baby in Case I. At that time she was coughing a great deal but had not reported her cough to the obstetrician, as she did not herself suspect that she had whooping-cough. This second baby began to cough on June 11 and whooped on June 15. The disease ran a moderately severe course for six weeks, the number of paroxysms varying from twelve to twenty in twenty-four hours at the height of the disease. When eight weeks old the baby weighed ten pounds four ounces and during the remainder of the first year thrived well, weighing twenty-two pounds when one year old.

Whooping-cough during the first month may be congenital, but the majority of cases are acquired. Cockayne states that Sir Thomas Watson described a case in which the disease was contracted before the patient was born, saying: "My bedmaker's daughter in Cambridge had a child ill with whooping-cough in the house with her during the last weeks of pregnancy and the newcomer whooped the first day he appeared in the world." Rilliet and Barthez, quoted by the same author, mention the case of a newborn child whose mother had had whooping-cough for a month and who had characteristic fits of coughing on the day of its birth. Blache reports a case as congenital in which the baby began to cough six days after birth, the mother having had whooping-cough, and who had contracted the disease from another child. This case may well be regarded as of doubtful congenital origin, as it would be more likely that the disease was contracted at the time of birth.

Cooper Cole has reported a case of whooping-cough in a premature infant. The mother who had developed very severe whooping-cough in the sixth month of pregnancy gave birth to a well-developed eight months' male infant on May 26. On May 29 the baby coughed for the first time. During the next fortnight the temperature ranged from 99° to 100° F. and the cough became more severe and paroxysmal until June 12, seventeen days after birth, when the child had a typical paroxysm ending in a whoop. For three weeks the paroxysms ranged from twelve to twenty-two daily. Recovery took place and at six months the patient was the equal of any other child of that age. The fact that the baby did not whoop until seventeen days after birth might cast some doubt on the congenital character of this case. That the incubation period of whooping-cough may be very short is shown by a case reported by Cockayne. In his case the baby began to cough on the

fifth day after birth, the disease being contracted from his brother, aged three and a half years, who was allowed to lie on the bed the day after birth and kissed both mother and baby. Bouchut has reported one case in which the infant began to cough two days after exposure. Frederici and Gerhart mention the fact that the incubation period of whooping-cough may be as short as two days, the average time in my own experience being ten to twelve days. With such a short incubation period occasionally occurring in whooping-cough considerable doubt would be cast on some of the cases reported as congenital. The writer cared for three mothers who have acquired whooping-cough in the last month of pregnancy without the babies showing any sign of the disease. When infection does occur it must be through the blood as is the case in congenital typhoid fever.

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EXPERIMENTAL STUDIES IN DIABETES:

SERIES II. THE INTERNAL PANCREATIC FUNCTION IN RELATION TO BODY MASS AND METABOLISM.

III. THE EFFECTS OF EXERCISE.

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AND

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THE preceding paper dealt particularly with the metabolism of matter, in the form of changes in the food supply and bodily reserves. The present paper is devoted to the metabolism of

energy as affected by exercise. It is recognized that the distinction is imperfect, since the energy of exercise must be furnished by combustion of material, which either demands increased food or causes undernutrition. Nevertheless, there is a difference, since the mere presence of stores of reserve fat was found to alter the assimilation, while exercise represents not only increased metabolism but also metabolism under a special stimulus.

Of the two factors chiefly concerned in carbohydrate combustion, one, the pancreas, was surgically reduced in Paper 1, and the other, the muscles, in Paper 2. Long-continued exercise builds up the muscles in mass and function. Athletes have a higher than average metabolism,¹ and the basal metabolism of a normal dog may fall as much as 16 per cent. in consequence of prolonged cage life.² As the dogs used in these experiments had mostly undergone many months of cage life, it is probable that the muscular factor in metabolism was considerably augmented by the exercise, and observations were therefore possible as to how far the development of this factor might compensate for deficiency of the pancreatic factor.

Mention has been made elsewhere³ of the early clinical work which indicated that exercise aids sugar combustion and diminishes glycosuria in mild diabetes, but is ineffective or even harmful in severe diabetes. Moraczewski⁴ found that exercise increased the blood sugar of normal persons and diabetics, while at the same time improved assimilation was manifest by a diminution of glycosuria. Mackenzie⁵ found a rise of 0.085 per cent. or less in the blood sugar of fasting totally depancreatized dogs with exercise, and a fall of 0.1 per cent. or less with exercise in depancreatized dogs receiving 200 gm. of meat and bread daily. The exercise periods were twenty to thirty minutes, and apparently irregularities of absorption and diuresis were not excluded as possible causes of the variations.

A preliminary outline of the present investigation and some observations on the application in clinical treatment have already been published.⁶ In the experiments here to be described, dogs were exercised under various conditions of fasting, feeding and intravenous glucose injections. The exercise consisted in hard running on a treadmill, driven entirely by the dog, with no measurement of the amount of work done. The animals mostly enjoyed the running, and it was considered sufficient that they were kept going at full speed for the periods specified. The method of discontinuous intravenous injections, described elsewhere,⁷ was adopted primarily with a view to the exercise experiments. The exposure of the jugular and other preparations were made some time in advance. Ordinarily, the glucose for each hour was given in the form of three injections, twenty minutes apart. With the dog

ready on the treadmill, catheterization, collection of the first blood sample and injection of the first dose of glucose were performed; next the animal ran for the specified time (generally fifteen minutes); a pause was made for the next blood sample and injection, and running was resumed.

The dogs were allowed water freely except in the experiments with intravenous injections. The volumes taken are omitted from the tables, because no differences in blood sugar were perceptible whether the animals chose to drink nothing or large quantities. Water was not given in the intravenous injection experiments and the animals were generally not thirsty.

The laboratory technic was the same as in the other papers, *i. e.*, Benedict's methods for sugar, the Fleischl-Miescher hemoglobin estimation, etc. The corpuscle volume was determined first in special capillary tubes of 12 cm. length, later in ordinary graduated centrifuge tubes. The blood was usually concentrated by exercise, but some allowances must be made for the limits of error in the methods.

TABLE I.—DOG C3-47. NORMAL. WEIGHT, 15.4 KGM. THE EFFECT OF EXERCISE ON NORMAL FASTING DOG.

Time.	Plasma sugar, per cent.	Hb., per cent.	Urine.		Rectal tempera- ture, °F.
			Volume, c.c.	Glucose, per cent.	
1 hr. before exercise. . . .	0.115	112	..	0	101.4
Immediately before exercise .	0.117	110	10	0	101.6
After 15 min. exercise	0.135	111	102.7
After ½ hr. exercise	0.176	111	104.1
After 1 hr. exercise	0.133	111	4	0	104.6
After resting 2 hrs. . . .	0.139	111	25	0	101.4

TABLE II.—DOG B2-90. NORMAL. WEIGHT, 33 KILOS.

Date, 1915.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Remarks.
Oct. 5	2.45 P.M.	0.111	65	Blood before exercise.
	3.30 .	0.154	66	After ¼ hr. of exercise; exercised to complete exhaustion.
Oct. 6	1.55 P.M.	0.111	64	Blood before exercise.
	2.00	0.154	79	After 5 min. of exercise.
	2.10	0.256	79	After 15 min. of exercise.
	2.25	0.216	68	After ½ hr. of exercise.
	2.55	0.108	60	After ½ hr. of rest.
	4.10	0.107	50	After 1½ hrs. of rest.

TABLE III.—DOG C3-49. NORMAL WEIGHT 16.9 KGM. COMPARISON ON NORMAL FASTING DOG OF EXERCISE, EXERCISE PLUS INTRAVENOUS GLUCOSE INJECTIONS, AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			Hemoglobin, per cent.			Urine volume, c.c.			Urine glucose, per cent.			Rectal temperature, °F.*			Remarks.
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	
Before injection	0.133	0.106	0.119	111	99	94	0	0	0	102.1	102.7	102.7	Exercise started.
1 hr. after 1st injection	0.154	0.166	0.167	120	94	80	..	20	10	..	1.00	1.54	103.8	104.6	102.8	
1 hr. after 2d injection	0.172	0.142	0.154	116	96	78	..	20	2	..	1.49	++	104.7	105.6	103.4	
1 hr. after 3d injection	0.125	0.122	0.134	110	98	76	15	25	55	0	++	0.15	
1 hr. after 3d injection	..	0.100	95	10	0	..	104.9	104.2	103.4	Exercise stopped.
1 hr. after 3d injection	..	0.133	95	25	0	104.7	..	
1 hr. after 3d injection	..	0.095	15	0	..	102.0	103.0	102.3	

1, exercise on fasting dog; II, exercise with intravenous glucose injections 1 gm. per kgm. per hr.; III, intravenous glucose injections 1 gm. per kgm. per hr. without exercise.

* High initial temperature due to hot weather.

TABLE IV.—DOG C3-54: NORMAL. WEIGHT, 19 KG.M. COMPARISON OF EXERCISE, EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS, AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			CO ₂ , volume per cent.			Hem. globin, per cent.			Urine volu. c. c.			Urine glucose, per cent.			Rectal temperature, °F.			Remarks.
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	
Before injection . . .	0.128	0.111	0.115	120	112	114	0	0	0	101.5	101.3	101.9	Exercise started.
15 min. after 1st injection	0.143	0.170	0.176	40.4	115	110	82	..	30	40	1.22	0.63	0.63	103.0	102.8	101.8	
15 min. after 2d injection	0.120	0.100	0.222	48.1	112	109	87	..	35	80	0.68	0.63	0.63	103.1	102.7	101.8	
15 min. after 3d injection	0.103	0.090	0.167	46.6	108	110	76	..	60	110	103.6	102.8	102.0	
15 min. after 4th injection	..	0.094	0.111	44.7	..	112	81	..	109	150	0	?	?	103.2	102.7	101.8	
1 hr. after 4th injection .	..	0.094	112	39	..	0	0	..	102.1	102.5	..	
1 hr. after 4th injection .	..	0.098	65	..	0	0	102.6	..	
15 min. after 5th injection	0.128	46.2	81	125	101.8	
1 hr. after 5th injection	0.105	46.2	81	63	101.9	
1 hr. after 5th injection	0.121	44.7	99	54	101.4	101.6	101.9	

I, exercise on fasting dog; II, exercise with intravenous glucose injections 1 gm. per kgm. per hr.; III, intravenous glucose injections 1 gm. per kgm. per hr. without exercise.

TABLE V.—DOG B2-00. PARTIALLY DEPANCREATIZED, NON-DIABETIC. WEIGHT 14 KGM. COMPARISON ON PARTIALLY DEPANCREATIZED DOG OF EXERCISE, EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS, AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			Hemoglobin, per cent.			Urine volume, c.c.			Urine glucose, per cent.			Rectal temperature, °F.			Remarks.
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	
1 hr. before injection	0.105	108	28	0	0	0	101.5	101.5	101.3	Exercise started.
Immediately before	0.125	0.108	0.105	102	104	112	103.4	103.2	..	
1 hr. after 1st injection	0.125	0.125	..	98	97	25	..	0.54	0.56	0.95	104.2	103.8	101.0	Exercise stopped.
1 hr. after 2d injection	0.133	0.101	0.288	95	95	98	..	19	90	0.50	103.7	102.8	101.6	
1 hr. after 3d injection	..	0.113	0.145	..	102	91	..	70	100	103.1	102.7	102.2	
1 hr. after 4th injection	0.105	0.089	0.091	98	95	93	6	120	175	0	102.0	102.3	102.2	
1 hr. after 4th injection	..	0.095	0.088	..	92	85	..	30	25	0	0	0	101.7	102.8	102.0	Exercise stopped.
1 hr. after 4th injection	..	0.130	0.098	..	92	80	..	25	30	
After resting 2 hrs.	0.112	95	160	0	0	0	

I, exercise on fasting dog; II, exercise with intravenous glucose injections 1 gm. per kgm. per hr.; III, intravenous glucose injections 1 gm. per kgm. per hr. without exercise.

TABLE VI.—DOG B2-01. NON-DIABETIC. WEIGHT 14 KGM. COMPARISON ON PARTIALLY DEPANCREATIZED DOG OF EXERCISE, EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS, AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			Hemoglobin, per cent.			Urine volume, c.c.			Urine glucose, per cent.			Rectal temperature, °F.			Remarks.
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	
1 hr. before injection	0.120	108	15	0	0	0	101.4	101.2	101.3	Exercise started.
Immediately before	0.125	0.099	0.111	108	101	108	0	0	0	101.4	101.2	101.3	
1 hr. after 1st injection	0.125	0.102	0.167	..	97	108	..	30	44	..	0.93	0.54	102.8	103.0	102.0	Exercise stopped.
1 hr. after 2d injection	0.133	0.127	0.176	107	97	90	..	20	55	..	0.84	0.89	103.2	102.6	102.2	
1 hr. after 3d injection	..	0.118	0.173	..	94	87	..	45	90	..	0.25	0.43	104.0	103.6	102.4	
1 hr. after 4th injection	0.150	0.094	0.154	106	90	80	10	60	100	0	0.34	+	103.8	103.0	102.3	
1 hr. after 4th injection	..	0.104	0.127	..	91	82	..	20	25	..	0	0	102.2	103.4	102.4	Exercise stopped.
1 hr. after 4th injection	..	0.115	0.110	..	85	89	..	10	30	0	0	0	101.9	103.7	102.6	

I, exercise on fasting dog; II, exercise with intravenous glucose injections 1 gm. per kgm. per hr.; III, intravenous glucose injections 1 gm. per kgm. per hr.

TABLE VII.—DOG B2-02. NON-DIABETIC. WEIGHT 10.5 KG. COMPARISON ON PARTIALLY DEPANCREATIZED DOG OF EXERCISE, EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS, AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			Hemoglobin, per cent.			Urine volume, c.c.			Urine glucose, per cent.			Rectal temperature, °F.			Remarks.
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	
1 hr. before injection	0.114	119	0	0	0	101.6	102.0	101.8	Exercise started.
Immediately before	0.115	0.105	0.111	119	120	115	3	101.6	102.0	101.8	
1/4 hr. after 1st injection	0.100	0.170	0.209	114	120	108	..	10	10	..	1.61	2.32	102.7	103.6	102.0	
1/4 hr. after 2d injection	0.111	0.118	0.271	101	116	106	..	8	25	..	0.60	2.13	103.8	104.2	101.7	Exercise stopped.
1/4 hr. after 3d injection	..	0.105	0.259	..	108	97	..	45	35	..	0.25	0.64	103.5	103.8	101.6	
1/4 hr. after 4th injection	0.108	0.101	0.200	101	105	104	4	50	12	0	0.35	..	103.6	104.0	101.6	
1/4 hr. after 4th injection	..	0.104	0.137	..	100	103	..	15	10	..	0	0	102.7	104.0	101.4	Exercise stopped.
1/4 hr. after 4th injection	..	0.128	0.125	..	96	99	..	10	10	..	0	0	101.5	103.8	101.7	

I, exercise on fasting dog; II, exercise with intravenous glucose injections 1 gm. per kgm. per hr.; III, intravenous glucose injections, 1 gm. per kgm. per hr. without exercise.

TABLE VIII.—DOG B2-71. WEIGHT, 16.8 KGM. MILD DIABETES.

Regular diet 1 kgm. lung, fed evenings. Improvement of assimilation of carbohydrate test-meal by exercise.

Date, 1915.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Remarks.
July 19	12.00 M.	0.099	81	28.7	Blood before exercise; fed 100 gm. bread.
	12.45 P.M.	0.100	106	45.0	After $\frac{1}{2}$ hr. of hard exercise.
	2.45	0.218	99	34.3	After resting 2 hrs.
	5.00	0.118	116	Ran hard most of afternoon; almost collapsed at close; no glycosuria.
July 21	12.30 P.M.	0.112	90	27.2	Before feeding 100 gm. bread. At rest.
	3.15	0.286	82	2 $\frac{1}{2}$ hrs. after feeding.
	5.30	0.286	..	32.5	5 hrs. after feeding; glycosuria 3.8 gm.
July 22	11.30 A.M.	0.124	82	32.2	Before exercise; exercised for 1 hr.; fed 100 gm. bread and exercise continued for $\frac{1}{2}$ hr., rested for 1 $\frac{1}{2}$ hrs.
	3.15 P.M.	0.109	89	36.5	After $\frac{1}{2}$ hr. of exercise.
	5.30	0.118	90	33.0	After 3 hrs. of exercise; no glycosuria.
July 23	12.15 P.M.	0.104	..	33.7	Blood before feeding 100 gm. bread; at rest.
	3.15	0.286	..	25.9	3 hrs. after feeding.
	5.45	0.149	..	36.0	5 $\frac{1}{2}$ hrs. after feeding; glycosuria 4.5 gm.
July 26	12.30 P.M.	0.118	82	32.1	Before feeding 50 gm. glucose; at rest.
	2.15	0.400	86	28.3	1 $\frac{1}{2}$ hrs. after feeding.
	4.00	0.189	93	32.1	3 $\frac{1}{2}$ hrs. after feeding.
	5.30	0.102	80	31.8	5 hrs. after feeding; glycosuria 3.6 gm.
July 27	12.30 P.M.	0.114	94	38.4	After 1 hr. of exercise; fed 50 gm. glucose.
	2.15	0.250	80	37.6	Exercised until 1.15; at rest until 1.50; exercised until 2.15.
	4.00	0.182	93	32.0	Ran hard all afternoon.
	5.30	0.143	104	36.0	Completely exhausted; glycosuria 0.3 gm.

TABLE IX.—DOG C3-66. WEIGHT, 20 KGM. SEVERE DIABETES. THE EFFECT OF EXERCISE ON FASTING DIABETIC DOG.

Time.	Plasma sugar, per cent.	Hb., per cent.	CO ₂ , vol. per cent.	Urine.		D:N ratio.
				Vol., c.c.	Glucose, per cent.	
Immediately before exercise	0.358	90	46.2	..	1.49	0.71
After $\frac{1}{2}$ hr. exercise	0.370	90	38.5
After 1 hr. exercise	0.455	84	34.7	2	Slight	..
After resting 1 hr.	0.435	73	46.2	34	3.13	4.05

TABLE X.—DOG B2-89. WEIGHT, 13.2 KGM. SEVERE DIABETES. COMPARISON ON PARTIALLY DEPANCREATIZED DOG, SEVERELY DIABETIC, OF EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.		Hemoglobin, per cent.		Urine volume, c.c.		Urine sugar, per cent.		Rectal temperature, °F.		Remarks.
	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	
Before injection . . .	0.133	0.122	117	112	0	0	101.8	101.2	Exercise started.
1 hr. after 1st injection . .	0.264	0.256	109	111	25	16	2.22	4.00	104.0	103.8	
1 hr. after 2d injection . .	0.400	0.333	93	100	52	30	3.30	5.00	104.0	104.9	
1 hr. after 2d injection . .	0.264	0.278	100	74	10	9	3.30	3.83	105.5	104.5	Exercise stopped.
1 hr. after 2d injection . .	0.218	0.250	105	76	5	4	+	0.40	105.0	103.9	
1 hr. after 2d injection . .	0.103	0.141	98	83	5	2	+	+	104.4	103.4	
1 1/2 hr. after 2d injection . .	0.131	0.122	86	78	6	4	0	++	102.5	104.2	

I, exercise with intravenous glucose injections, 1 gm. per kgm. per hr.; II, intravenous glucose injections, 1 gm. per kgm. per hr. without exercise.

TABLE XI.—DOG B2-79. WEIGHT 15 KGM. INCREASINGLY SEVERE DIABETES.

Date.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	CO ₂ , vol. per cent.	Urine sugar, per cent.	Remarks.
1915.							
July 17	10.30 A.M.	0.133	100	46.2	Blood taken before exercise.
	12.30 P.M.	0.100	120	49.0	After exercising hard for 2 hrs.
July 23	2.30 P.M.	0.109	105	45.3	Before exercise.
	6.00	0.105	125	49.5	After 3½ hrs. hard exercise.
Sept. 25	12.15 P.M.	0.169	110	50.0	After 5 min. of exercise.
	1.10	0.143	110	52.0	After 1 hr. of exercise.
Dec. 1	10.40 A.M.	0.278	111	43.5	..	1.03	Before exercise; fasting.
	1.40 P.M.	0.278	104	40.0	..	0.25	Immediately before exercise.
Dec. 6	1.50	0.313	108	48.5	After 10 min. of exercise.
	2.05	0.159	98	After 25 min. of exercise.
	2.40	0.143	97	After 1 hr. of exercise.
	3.40	0.256	97	41.0	..	Faint	After 2 hrs. of exercise.
	1.50 P.M.	0.200	0	Before exercise fed 500 gm. lung; allowed to rest ½ hr. before exercise.
	4.50 P.M.	0.208	Slight	After 2½ hrs. of exercise.
1916.							
Feb. 3	1.50 P.M.	0.278	95	Very faint	1 hr. before exercise; fasting.
	2.50	0.334	95	Very faint	Immediately before exercise.
Mar. 30	3.05	0.264	98	After 15 min. of exercise.
	3.20	0.304	103	After ½ hr. of exercise.
	3.50	0.278	105	Slight	After 1 hr. of exercise.
	4.50	0.294	0	After resting 1 hr.
	3.20 P.M.	0.455	90	..	42.3	0.61	Before exercise; fasting; D:N ratio 1.90.
	3.50	0.312	82	..	31.9	..	After ½ hr. of exercise.
	4.20	0.435	72	..	34.7	0.97	After 1 hr. of exercise; D:N ratio 6.45.
	5.20	0.435	72	..	42.3	0.78	After resting 1 hr.; D:N ratio 2.30.

DOG B2-79. (TABLES XI AND XII AND CHART III.)

Dog B2-79, as described in the preceding paper, was fattened so as to produce steady aggravation of the diabetes, while the successive recurrences of glycosuria were checked by reduction of protein and substitution of fat. Table XI illustrates the effects of exercise in the different stages of progress on days without feeding. On July 17 and 23 the plasma sugar was low and was reduced a trifle by exercise. On September 25 hyperglycemia was present but was lowered by exercise. On December 1 the hyperglycemia was greater; it rose sharply with ten minutes of exercise, then fell during the first hour, but showed a rising tendency at the end of the second hour. On December 6 exercise seemed to prevent the usual rise of blood sugar after protein feeding, but it is possible that digestion was delayed. On February 3 fluctuations of the hyperglycemia occurred, but any effect of exercise is doubtful.

TABLE XII.—DOG B2-79.

Time.	Nov. 8.			Nov. 11.			Nov. 12.			Nov. 26.	Nov. 29.
	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Plasma sugar, per cent.	Plasma sugar, per cent.
Before exercise or food	0.125	116	53.0	0.161	115	57.8	0.115	109	40.0	0.156	0.154
3 hr. after food	0.142	110	50.0	0.133	115	50.0	0.115	105	41.0		
1 hr. after food	0.184	112	51.0	0.142	113	44.0					
1½ hr. after food	0.167	114		0.130	109	51.0	0.108	105	44.5		
3 hr. after food	0.128	112	58.0	0.139	100	47.5	0.111			0.182	
4 hr. after food	0.147	114	51.0								
5 hr. after food	0.141	109	65.0							0.250	0.208

A, fed 500 gm. lung; Nov. 8, at rest; Nov. 11 and 12, with exercise. B, fed 1 kgm. lung; Nov. 26, at rest; Nov. 29, with exercise.

On March 30 there was a fall of plasma sugar, particularly after thirty minutes of exercise, but the actual effect was injury rather than benefit, as shown in the extra sweeping out of sugar represented in the D:N ratios.

Table XII shows protein-feeding experiments on the same dog during November, 1915. A real improvement of assimilation with exercise at this stage, as opposed to a mere slowing of food absorption, is indicated by the fact that the plasma sugar elevations were longer as well as higher on rest days, and also on a second exercise day (November 12) were lower than on the day before. There was no glycosuria.

DOG B2-80. (TABLE XIII AND CHART V.)

Dog B2-80, as described in the preceding paper, progressed to severe diabetes and acidosis on excessive feeding, particularly with fat. Toward the end exercise was tried on several days. The dog was strong and willing and ran hard. The plasma sugar was increased rather than diminished. The rectal temperature rose as usual above 104° F. during exercise. Acidosis was present throughout, as indicated by nitroprusside reactions in blood and urine and rather low plasma bicarbonate values, but the former did not increase and for some reason the bicarbonate concentration actually rose with the running. There were also no coma symptoms even when the dog ran to exhaustion. This was the more remarkable because coma was so near. No exercise was used after August 8 and the condition appeared unchanged. Vomiting began on August 11, and coma on August 13.

TABLE XIII.—DOG B2-80. WEIGHT, 17 KGM.

Date.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Urine.		Remarks.
					Vol., c.c.	Sugar, per cent.	
July 23	2.30 P.M.	0.263	114	49.0	Before exercise; fasting.
	6.15	0.270	120	55.5	After 3½ hrs. of hard exercise
July 26	11.30 A.M.	0.208	118	50.3	Before exercise.
	12.30 P.M.	0.208	125	53.6	After 1 hr. of exercise.
Aug. 8	10.50 A.M.	0.294	103	55.0	..	0.66	Before exercise.
	11.00	0.294	101	56.0	6	0.56	After 10 min. of hard exercise.
	12.20 P.M.	0.322	94	61.0	9	1.67	After resting 1 hr. 20 min.
	12.50	0.333	105	64.5	5	1.23	After ¼ hr. of very hard exercise; exhausted.
	4.30	0.303	104	53.4	16	1.25	After resting 3 hrs. 40 min.

DOG C3-18. (TABLE XIV AND CHART V.)

Dog C3-18 was a graft animal with diabetes, like dog C3-02. The period covered in Table XIV represents gain in tolerance, apparently due in part to exercise. There was a fixed diet of beef-lung and pancreas, on which the body weight declined by about three-fourths of a kilo during this period, so that part of the improve-

ment of assimilation may be attributed to undernutrition; but the exercise must also have contributed toward the undernutrition.

On November 15 exercise failed to prevent a great rise of blood sugar after feeding or stop the existing glycosuria. November 16 the initial blood sugar was higher but did not rise during one and a half hours. November 17 the urine was free from sugar. With continuous rest thereafter, except for a single exercise day on November 19, glycosuria remained absent through November 23. It was present on November 24, 25 and 26 and ceased with a single exercise day on November 26. The table shows a rise of blood sugar after feeding on the rest day November 27 and none on the exercise day November 26. Glycosuria remained absent. On November 29 exercise reduced the blood sugar. The dog was fed that evening, but not on November 30. On December 1 the blood sugar fell during two hours of exercise and rose during the ensuing one and a half hours of rest.

The record suggests not only that exercise facilitated assimilation, but also that it was more effective after the tolerance had been improved by undernutrition. (See also Chart V.)

TABLE XIV.—DOG C3-18. WEIGHT, 15 KGM.

Date.	Hour.	Plasma sugar, per cent.	Urine sugar, gm. in 24 hours.	Remarks.
1915.				
Nov. 15	10.35 A.M.	0.188	2.94	Blood taken before exercise; fed usual diet.
	11.30	0.256	After 20 min. of exercise; rather weak; cannot be exercised long at a time.
Nov. 16	2.50 P.M.	0.555	After resting 3½ hrs.
	9.45 A.M.	0.238	0	Before exercise; fasting.
	10.15	0.222	After ½ hr. of exercise; exercise stopped.
	10.35	0.222	After resting ½ hr.; exercise started.
	11.05	0.238	After ½ hr. of exercise; urine for the period 12 c.c.; negative sugar.
Nov. 26	2.00 P.M.	0.186	0	Before exercise; fed usual diet.
	4.30	0.182	After 2½ hrs. of exercise.
Nov. 27	1.00 P.M.	0.208	0	Before feeding; fed usual diet; at rest.
	3.30 P.M.	0.262	After resting 2½ hrs.
Nov. 29	1.55 P.M.	0.218	0	Before exercise.
	3.30	0.147	After 1½ hrs. of exercise.
Dec. 1	10.10 A.M.	0.196	0	Fasting for 36 hrs.; blood taken before exercise.
	12.10 P.M.	0.162	After two hrs. of exercise.
	1.45	0.196	After resting 1½ hrs.; urine for the period 95 c.c.; negative sugar.

DOG C3-22. (TABLE XVI AND CHART V.)

Dog C3-22. Severe diabetes, controlled four months by diet, first 1 kilo of lung, then 400 gm. lung and 200 gm. suet, then 300 gm. lung and 200 gm. suet, then 200 gm. lung and 200 gm. suet. The recurrences of glycosuria were checked each time by the reduction of protein, but the usual gradual aggravation occurred on the high calory diets, and at the time of these experiments glycosuria

TABLE XV.—DOG C3-19. SEVERE DIABETES.

Date.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Urine sugar, per cent.	Remarks.
Aug. 11	3.00 P.M.	0.250	87	36.7	0	Before feeding 500 gm. lung; at rest.
	6.00	0.276	80	35.2	3.84	3 hrs. after feeding.
	11.30	0.303	90	34.6	6.66	8½ hrs. after feeding; glucose excreted 6.4 gm.
Aug. 12	12.00 M.	0.294	85	35.0	2.22	Before exercise; fed 500 gm. lung.
	12.40 P.M.	0.345	Exercised from 12.15 to 12.40; glucose excreted before exercise 3.5 gm.
	1.00	0.286	98	40.0	2.27	Exercised from 12.45 to 1; glucose excreted after exercise 2.3 gm.
	3.00	0.263	88	31.5	1.58	After alternate rest and exercise periods.
	8.45	0.192	84	30.2	0.75	Exercised until 6.30, rest thereafter.

Dog C3-19, weighing 11.1 kilos, tolerated 500 gm. lung on August 9 without glycosuria, but showed glycosuria of 1.1 gm. on August 10. On the two following days rest and exercise were compared with results shown in Table XV. The increasing glycosuria was arrested by exercise, inasmuch as 3.5 gm. glucose was excreted during the forenoon of August 12 without exercise or food, and only 2.3 gm. during the remainder of the twenty-four hours with feeding and exercise.

TABLE XVI.—DOG C3-22. NORMAL WEIGHT, 13.4 KGM. SEVERE DIABETES.

Date.	Hour.	Plasma sugar, per cent.	Urine sugar, gm. in 24 hours.	Remarks.
1915.				
Nov. 12	10.15 A.M.	0.222	Faint	Before exercise; fed usual diet.
	11.20	0.238	After 1 hr. of exercise.
	3.00 P.M.	0.322	3.1	After 3½ hrs. of rest.
Nov. 13	2.00 P.M.	0.145	1.6	Before exercise; fasting.
	3.00	0.125	After 1 hr. of exercise.
	4.00	0.125	After 2 hrs. of exercise.
Nov. 14	Slight	Rest day.
Nov. 15	10.25 A.M.	0.200	1.7	Before exercise; fed usual diet.
	12.00 M.	0.250	After 1 hr. of exercise.
	1.30 P.M.	0.263	After resting 1½ hrs.
	2.30	0.182	After 1 hr. of exercise.
	3.00	0.170	After 1½ hrs. of exercise.
	4.20	0.257	After resting 1 hr. 20 min.
Nov. 16	9.35 A.M.	0.159	Faint	Before exercise; fasting.
	10.35	0.154	After 1 hr. of exercise.
	11.35	0.154	After 2 hr. of exercise.
Nov. 26	2.05 P.M.	0.227	Faint	Before exercise; fed usual diet.
	4.30	0.186	After 2¼ hrs. of exercise.
Nov. 27	10.50 A.M.	0.256	1.3	Fed usual diet; no exercise.
	2.50 P.M.	0.400	4 hrs. after feeding.
Nov. 28	1.1	Exercise day.
Nov. 29	1.55 P.M.	0.227	0.3	Before exercise; fasting.
	3.30	0.170	After 1½ hrs. of exercise.
Nov. 30	Fast day.
Dec. 1	10.10 A.M.	0.200	0	Before exercise; fasting.
	12.10 P.M.	0.128	After 2 hrs. of exercise.
	1.45	0.200	After resting 1 hr. 35 min.
Dec. 6	1.50 P.M.	0.313	1.2	Before exercise; fed usual diet; rested ½ hr. before beginning exercise.
	4.50	0.500	After 2½ hrs. of exercise.
Dec. 7	2.7	Rest day.
Dec. 8	3.5	Rest day.
Dec. 9	13.6	Rest day.

was returning on the diet last mentioned. Exercise was begun November 12 in the attempt to stop the downward progress. The weight was then 11.5 kgm.

November 12, hyperglycemia increased after feeding notwithstanding exercise, but by the next day there was reduction of hyperglycemia and glycosuria. Both were found higher on November 15, after the preceding rest day, but an alternation of rest and exercise (November 15) showed that exercise reduced the blood sugar. On November 16 the fasting blood sugar was lower but was not appreciably reduced by exercise. Hard exercise was then given every day, both before and after feeding, through November 19; no blood sugar analyses were made, but glycosuria remained absent.

Beginning November 20 the dog remained at rest. Traces of glycosuria began November 25 and increased the next day. On that day (November 26) exercise was given; the blood sugar was lowered and the glycosuria remained too small to titrate. November 27 was a control day without exercise and showed a marked rise of blood and urine sugars as compared with November 26.

Exercise was then continued and reduced the glycosuria but failed to abolish it until the fast day of November 30. The regular diet of 200 gm. lung and 200 gm. suet then continued, with the hardest possible exercise occupying the greater part of every day. Nevertheless, traces of glycosuria began December 2 and gradually increased to 1.2 gm. on December 6. Exercise thus finally failed to suppress hyperglycemia and glycosuria, but evidently restrained them somewhat, as shown by the rapid increase with discontinuance of exercise following December 6.

DOG C3-02. (TABLE XVII.)

Dog C3-02 was an animal with moderate diabetes, having no pancreas tissue except a subcutaneous graft, of which the pedicle had been cut so as to isolate it from all intra-abdominal connections. Table XVII shows that exercise had the usual effect in restraining the rise of blood sugar after feeding, and thus excludes any nervous influence upon the pancreas as the cause of this action.

TABLE XVII.—DOG C3-02. SUBCUTANEOUS GRAFT.

Date.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Rectal temp., ° F.	Remarks.
1915. Aug. 10	11.30 A.M.	0.120	95		Blood taken; dog allowed to rest quietly in cage.
	3.30 P.M.	0.145	91	..	Blood taken after resting 4 hrs.; fed 600 gm. lung, 600 gm. raw pancreas and 100 gm. suet.
	6.00	0.286	100	..	Blood taken 2½ hrs. after eating.
Aug. 11	12.25 P.M.	0.139	88	102.4	Blood taken before exercise.
	1.00	0.154	97	103.5	After ½ hr. of exercise.
	3.30	0.164	98	..	After 2½ hrs. of rest; fed same diet as on Aug. 10.
	4.30	0.151	..	104.8	After 1 hr. of exercise.
	6.00	0.164	..	105.5	After 2½ hrs. of exercise.

TABLE XIX.—DOG C3-53. WEIGHT 12.3 KGM. THE EFFECT OF EXERCISE ON A PHLORIZINIZED DOG.

Time.	Dec. 27, before giving phlorizin.					Dec. 28, phlorizin and exercise.					Dec. 29, phlorizin and exercise.					Dec. 30, phlorizin without exercise.				
	Plasma sugar, per cent.	Hb., per cent.	Urine.		Plasma sugar, per cent.	Hb., per cent.	Urine.		Plasma sugar, per cent.	Hb., per cent.	Urine.		Plasma sugar, per cent.	Hb., per cent.	Urine.		Plasma sugar, per cent.	Hb., per cent.	Urine.	
			Vol., c.c.	Sugar, per cent.			Vol., c.c.	Sugar, per cent.			Vol., c.c.	Sugar, per cent.			Vol., c.c.	Sugar, per cent.			Vol., c.c.	Sugar, per cent.
1 hr. before exercise . . .	0.111	112	45	0	0.097	106	28	7.15	0.077	101	290	7.82	0.095	86	124	0.60				
Immediately before exercise	0.112	106	25	7.70	0.092	110	25	8.25	0.083	86	14	6.72				
After 15 min. of exercise	0.159	110	0.082	104				
After ½ hr. of exercise	0.119	108	0.119	100				
After 1 hr. of exercise	0.125	95	20	9.10	0.132	108	25	10.0				
After resting 2 hrs.	0.118	92	55	7.70	0.100	95	175	2.5	0.081*	..	67*	6.62*				
After resting 5 hrs.	0.108	106	50	7.70	0.072	..	75	5.5				

* Taken 2½ hours after previous blood, dog at rest all the time.

TABLE XXI.—DOG C3-57. WEIGHT 14 KGM. PHLORIZINIZED.

Time.	Blood.				Urine.				Remarks.
	Plasma sugar, per cent.	Hb., per cent.	CO ₂ vol. per cent.	Nitro-prusside reaction.	Volume, c.c.	Sugar, per cent.	D:N ratio.	Nitro-prusside reaction.	
Mar. 2.									
8.00 A.M. . .	0.065	92	41.4	Faint	..	3.03	3.24	Very heavy	Started exercise. Exercise finished; some urine lost on treadmill. 10.50 finished 1st intravenous glucose 0.5 gm. per kgm. and exercise started. 11.20 finished 2d injection. 11.58 finished 3d injection. Urine lost on treadmill; exercise stopped.
11.00 A.M. . .	0.080	95	41.4	Faint	54	3.70	3.80	Very heavy	
11.30 A.M. . .	0.095	108	33.8	Faint					
12.00 M. . .	0.087	105	36.6	Slight	6	3.57	4.26	Heavy	
Mar. 3.									
10.40 A.M. . .	0.056	112	40.4	Slight	..	5.90	..	Mod.	
11.05 A.M. . .	0.182	..	39.5	0	14	6.25	..	Faint	
11.40 A.M. . .	0.161	90	33.8	0	24	4.00	..	0	
12.15 P.M. . .	0.250	98	36.6	0	19	2.50	..	0	
12.30 P.M. . .	0.118	92	38.5	0	8	2.78	..	0	

Note on Tables XIX, XX and XXI.

These fasting dogs received 1 gm. phlorizin in oil suspension subcutaneously daily. Mobilization of extra sugar is indicated by the rise of blood sugar and also of the D:N ratios, according to the principles made familiar by Lusk. It may further be noted (Dog C3-57) that the absolute sugar excretion was diminished, at least for the brief experimental period, by reduction of the volume of urine by exercise. It was not determined whether the intravenously injected glucose was quantitatively excreted, but the nitroprusside reactions in blood plasma and urine were cleared up.

THERAPEUTIC RESULTS OF LONG-CONTINUED EXERCISE.

Dog B2-86.

Dog B2-86 was described in Paper 2 of Series I⁸ as an animal in which prolonged maximal feeding of starch and sugar barely failed to break down the tolerance. In this and a series of similar dogs the attempt was made to keep up the failing appetite with exercise, in the hope that the tolerance might finally break down, but the existing glycosuria merely cleared up more quickly and remained absent. Prolonged overfeeding with exercise therefore failed to produce diabetes in dogs which were non-diabetic on feeding alone.

Dog B2-43. (TABLE XXII.)

Dog B2-43 was an animal with mild diabetes, free from glycosuria on a diet of 1 kilo of lung, fed evenings, but with a limited tolerance for bread, as shown in the experiments in Paper 2 of Series I. In July, 1915, experiments were performed, indicating a better assimilation of carbohydrate test-meals on exercise days than on rest days, as shown in Table XXII. The weight during this time was stationary at 10.5 kilos.

After a few experiments with cold, as described in a later paper, the dog was left at rest, and a beneficial after-effect of the exercise was indicated by the continued absence of glycosuria on the diet of 1 kilo lung and 100 gm. bread. On this diet without exercise the weight rose to 12 kilos by August 31, when glycosuria began with 0.7 per cent. sugar in 450 c.c. urine, increasing to 1.4 per cent. in 419 c.c. urine on September 1. With exercise this glycosuria immediately dropped to faint traces and ceased September 2. Exercise was then continued to the extent of an hour or two daily after the carbohydrate feeding; glycosuria thus remained absent while the weight rose to 12.8 kilos by September 10.

With omission of exercise, September 10 to 17, there was daily glycosuria from 0.16 to 0.9 per cent., while the weight rose to 14 kilos.

Heavy exercise was then resumed and at the same time the bread increased to 150 gm. daily. The weight thus gradually fell to 11.8 kilos on October 6 and glycosuria was continuously absent. On October 6 the bread was increased to 250 gm., still without glycosuria, but the dog now left most of the lung uneaten, and the weight thus fell further to 10.6 kilos on October 20.

Exercise was then stopped and 100 gm. lard added to the diet. Glycosuria remained absent, even though the weight gradually rose to 14.5 kilos by the following March. With an unlimited diet of bread only, the glycosuria then returned.

The final marked improvement was doubtless due largely to recuperation in the pancreas remnant, but this was evidently favored by exercise. Though the earlier experiments indicated that exercise favored assimilation even when the weight rose, the benefit was doubtless greater when the weight was reduced. It may be inferred that reduction of weight is beneficial even when it is produced by the increased metabolism of exercise instead of by reduction of the food supply.

TABLE XXII.—DOG B2-43. MILD DIABETES.

Date.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Remarks.
July 17	9.30 A.M.	0.111	98	43.7	Started exercise; fasting.
	11.00	0.106	99	39.3	After 1½ hrs. of exercise.
July 19	12.00 M.	0.118	104	43.0	Blood taken before feeding 100 gm. bread; 12.15 started exercise.
	12.45 P.M.	0.118	83	43.0	After ½ hr. of exercise.
	2.30	0.228	95	40.0	After resting 1½ hrs.
	5.00	0.085	98	40.5	After 2½ hrs. of exercise.
July 21	12.30 P.M.	0.133	90	43.5	Before feeding 100 gm. bread; at rest.
	3.00	0.178	96	45.0	2½ hrs. after feeding.
	5.30	0.222	..	37.1	5 hrs. after feeding.
July 22	12.30 P.M.	0.125	97	38.0	After 1 hr. of exercise, fed 100 gm. bread; exercised until 1 P.M.
	3.15	0.115	94	38.5	Rested in cage until 2.30, then started exercise; blood taken after ¼ hr. of exercise.
	5.30	0.111	96	37.5	After 3 hrs. of exercise.
July 23	12.15 P.M.	0.125	96	37.3	Before feeding 100 gm. bread; at rest.
	3.15	0.217	93	37.0	3 hrs. after feeding.
	5.45	0.133	..	35.3	5½ hrs. after feeding.
July 24	12.00 M.	0.128	86	40.8	After 2 hrs. of exercise; fed 100 gm. of bread and by mistake 1 kgm. lung; rested remainder of day.
	3.15 P.M.	0.244	91	40.8	3¼ hrs. after feeding.
	5.30	0.270	81	38.0	5½ hrs. after feeding.
July 26	12.00 M.	0.115	83	35.0	Before feeding 50 gm. glucose.
	1.45 P.M.	0.294	92	36.5	1½ hrs. after feeding.
	4.00	0.112	80	37.0	4 hrs. after feeding.
	5.30	0.137	88	36.0	5½ hrs. after feeding.
July 27	12.30 P.M.	0.156	95	37.0	After ¼ hrs. of exercise; 12.30 P.M. fed 50 gm. glucose.
	2.15	0.123	84	35.0	Exercise continued to 1.15, rested in cage to 2.15.
	4.30	0.107	70	45.0	
	6.00	0.100	73	37.8	Exercised from 2.15 to 6.00 P.M.

DOG B2-88. (TABLES XXIII AND XXIV AND CHART IV.)

Dog B2-88 was mildly diabetic three months after operation, sugar-free on 1 kilo of beef-lung daily, but with glycosuria between 1 and 2 per cent. with 100 gm. bread. At this stage (July 12, 1915), at a weight of 12 kilos, 25 gm. bread was added to the diet

and exercise begun. With increasing exercise the bread was increased to 50 gm. on July 18 and to 100 gm. on July 27 without glycosuria.

TABLE XXIII.—DOG B2-88. MODERATE DIABETES.

Time.	Plasma sugar, per cent.					
	Nov. 9.	Nov. 10.	Nov. 11.	Nov. 12.	Nov. 18.	Nov. 27.
Before exercise or feeding .	0.189	0.114	0.122	0.122	0.143	0.137
After $\frac{1}{4}$ hr. of exercise	0.135		
After $\frac{1}{2}$ hr. of exercise	0.125		
After 1 hr. of exercise	0.112		
$\frac{1}{4}$ hr. after eating . . .	0.169	0.143	0.154
$\frac{1}{2}$ hr. after eating . . .	0.250	0.147	0.173
$\frac{3}{4}$ hr. after eating	0.149		
1 hr. after eating . . .	0.257	0.133	0.167	0.145	0.166	0.257
1 $\frac{1}{2}$ hr. after eating	0.143		
2 hrs. after eating	0.154	0.143		
3 hrs. after eating . . .	0.257	0.200	0.137	0.156	0.222	0.333
4 $\frac{1}{2}$ hrs. after eating	0.154		

A test diet of 200 gm. bread and 100 gm. lung was fed on the six days mentioned, without glycosuria. November 9 and 27 were rest days. On November 10, 11 and 18 exercise was begun immediately after feeding, and resulted in lower blood sugar curves than on the control days. On November 12 exercise was given for one hour before feeding and the dog then left at rest after feeding. The blood sugar curve seemed to indicate a beneficial after-effect of the exercise upon assimilation.

July 28 exercise was omitted and there was immediate glycosuria of 6.2 gm. in the ensuing twenty-four hours. July 29 the same diet was taken with exercise without glycosuria. There was the usual curve of hyperglycemia on July 28, while on July 29 the plasma sugar did not go above 0.128 per cent. Exercise thus permitted assimilation of 100 gm. bread, though the weight meanwhile had risen to 12.8 kilos.

As a further control to exclude a spontaneous rise of tolerance both bread and exercise were omitted for a month. Then at an increased weight of 13.6 kilos the addition of 100 gm. bread on August 30 caused glycosuria of 0.4 per cent. in 761 c.c. urine, increasing the next day to 1.2 per cent. in 724 c.c. With exercise the sugar excretion was halved on September 1 and absent September 2.

The dog was strong and fond of running and by harder exercise it was possible to increase the bread to 150 gm., though the weight rose gradually, and traces of glycosuria were present whenever the exercise was relaxed a little. By September 28 the weight had reached 14.8 kilos and the bread was increased to 200 gm. Traces of glycosuria were present during the ensuing week and were stopped by increasing exercise, so that the dog spent the greater part of every day on the treadmill. Meanwhile much of the lung of the diet was left uneaten and the weight by October 20 had fallen to 13.3 kilos.

TABLE XXIV.—DOG. B2-88. MODERATELY DIABETIC. COMPARISON OF EXERCISE, EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS, 1 GM. PER KG. PER HR., AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			Hemoglobin, per cent.			Urine volume, c.c.			Urine glucose, per cent.			Rectal temperature, °F.		
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.
Before injection	0.143	0.161	0.118	107	0	0	0	101.6
1 hr. after 1st injection	0.156	0.200	0.200	93	15	120	..	0	0	0	101.1
1 hr. after 2d injection	0.189	0.200	0.200	91	10	64	..	0	0	0	101.0
1 hr. after 3d injection	..	0.164	0.232	94	4	73	..	0	0	0	101.2
1 hr. after 4th injection	0.161	0.147	0.192	85	10	100	0	0	0	0	101.6
1 hr. after 5th injection	..	0.126	0.200	82	5	106	..	0	0	0	101.6
1 hr. after 6th injection	..	0.118	0.200	89	17	64	..	0	0	0	101.4
1 hr. after 7th injection	..	0.112	0.200	91	20	90	..	0	0	0	101.5
1 hr. after 8th injection	..	0.121	0.128	20	110	..	0	0	0
1 hr. after 9th injection	..	0.105	0.112	20	117	..	0	0	0
1 hr. after 10th injection	..	0.133	0.121	16	0	0	0

I, Nov. 20, 1915, exercise fasting; II, Dec. 2, exercise with intravenous glucose injections, 1 gm. per kgm. per hr.; III, Dec. 7, intravenous glucose injections, 1 gm. per kgm. per hr.

Exercise was then stopped and a diet begun of 200 gm. bread, 100 gm. lard and only 200 gm. lung. November 5, at a weight of 14.1 kilos, glycosuria appeared (0.34 per cent. in 780 c.c. urine), and increased on the following day to 0.95 per cent. in 620 c.c. It was abolished by a fast day on November 7. This control proved that the preceding absence of glycosuria had not been due to the reduced protein intake.

Exercise was then omitted except for a series of tests, most of which are shown in Tables XXIII and XXIV and Chart IV. It was evident from these that exercise retained its power to diminish hyperglycemia even after long usage.

Subsequently, without exercise, on a diet of 200 gm. bread and 100 gm. lung with such lard as might be eaten, there was gradual increase of weight without glycosuria but with increasing hyperglycemia. April 10, 1916, at a weight of 16 kgm., glycosuria appeared and rapidly increased in a more threatening manner than before, reaching 4.5 per cent. The heaviest exercise was then unable to stop it, though it ceased promptly with omission of bread or with single fast days. April 22 to 30 glycosuria was kept absent by carbohydrate-free diet in order to give a fresh start, but with addition of the 200 gm. bread there was again heavy glycosuria in spite of exercise.

Beginning May 5 exercise and reduction of the bread ration to 100 gm. kept glycosuria absent and reduced the weight to 14.3 kgm. Nevertheless, glycosuria appeared on May 14 and 15, was temporarily checked by increased exercise, but reappeared May 18 and resisted exercise.

Exercise and carbohydrate were then omitted, and on regulated diet the weight was gradually reduced by August 16 to 13.2 kilos. Though the tolerance at this weight had formerly been so high, marked glycosuria now resulted, even after the long interval allowed for recuperation, from the addition of as little as 25 gm. bread. With exercise this glycosuria was promptly abolished and remained absent on a diet of 200 gm. lung, 100 gm. suet and 25 gm. bread until September 12, when it reappeared at a weight of 13.6 kilos.

Bread was then omitted and glycosuria stopped, but hyperglycemia continued notwithstanding exercise. October 18, though the weight had fallen to 12.8 kilos, the increasing hyperglycemia and beginning of acidosis gave warning that the diabetes had reached a dangerous stage. The experiment was therefore ended and an attempt made to save the animal. It proved impossible to restore tolerance for any living diet, and death finally occurred February 25, 1917, at a weight of 8 kilos.

This experiment had been planned for testing the practical benefits of exercise in clinical treatment. It showed (1) that

exercise favors carbohydrate assimilation even over long periods, especially in mild diabetes; (2) that it loses its effectiveness not with time but with increasing severity of the diabetes; (3) that it can atone to some extent for indiscretions in diet and weight but cannot safely be used as a substitute for dietary restriction, and the attempt to force the diet to the utmost and burn up the surplus calories with exercise ends finally in disaster.

Conclusions. 1. The influence of exercise on carbohydrate assimilation was traced from the normal through various stages of impairment. A rise of plasma sugar, presumably representing increased transportation, ordinarily accompanies exercise in the normal animal, and the assimilation for test doses of glucose is increased. In mild diabetes, when there is a tendency to abnormal hyperglycemia from defective assimilation of carbohydrate, exercise markedly diminishes the hyperglycemia and glycosuria and facilitates utilization. This power of exercise to improve assimilation applies to the glucose formed from protein diets or body stores as well as from preformed carbohydrate. It does not depend upon the febrile temperatures which attend heavy exercise in dogs, for equal results were obtained in human patients without important elevations of temperature. It is not lost with long usage but becomes less as the diabetes becomes more severe. At a certain advanced stage exercise is unable to modify hyperglycemia or glycosuria. Beyond this, in the extreme forms of diabetes in partially depancreatized animals and in totally depancreatized animals, the extra mobilization of sugar by exercise results in an actual increase of glycosuria and of the D:N ratio.

2. With regard to diabetic theory, these results seem to indicate: (a) That the increased metabolism of exercise does not impose an added strain upon the internal pancreatic function; (b) that the combustion of food materials through the increased muscular metabolism and mass resulting from exercise is a definite relief to the internal pancreatic function as compared with the accumulation of such materials through inactivity; (c) that the internal pancreatic secretion is nevertheless an indispensable intermediary in such combustion, and that exercise merely enables the muscles to make more active use of such quantity of this secretion as is available to them but cannot compensate when this quantity falls below the necessary minimum.

3. For purposes of practical treatment the combustion of food by exercise is preferable to its deposit in the body, but exercise cannot replace dietary restriction or permanently atone for excessive diets. The fundamental value of exercise is probably as a form of undernutrition. The combustion of calories by exercise, however, is not as beneficial as omitting them from the diet, and loses its potency at a stage when dietetic undernutrition is still effective.

Impairment of sugar utilization by exercise occurs only in the extreme stages of diabetes, but in human patients the nervous and systemic influences must also be considered. With any important degree of undernutrition heavy exercise involves undesirable fatigue and strain, but light exercise aids health. Rest is necessary in the severest cases. In the clinical application, therefore, dependence for the actual control of the diabetes is placed upon diet, and exercise is limited to the requirements of comfort and hygiene. The thorough dietetic treatment thus involves two changes from former practice: on the one hand heavy exercise as advocated by the earlier clinicians for burning up surplus sugar is discouraged; on the other hand the hygienic benefits of lighter exercise are made available to many patients to whom exercise was formerly forbidden.

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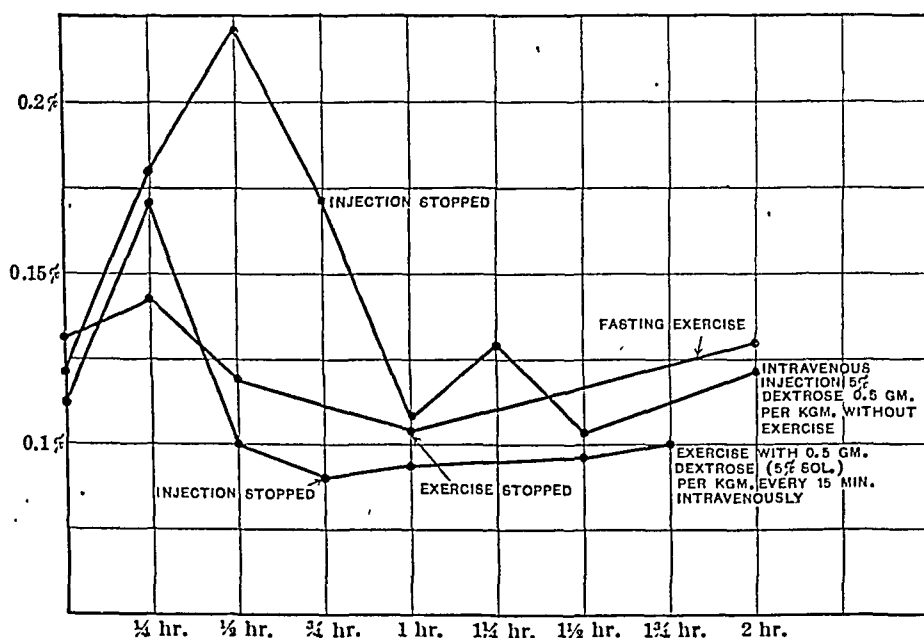


CHART I.—Dog C3-54. Normal. Weight 19 kgm.

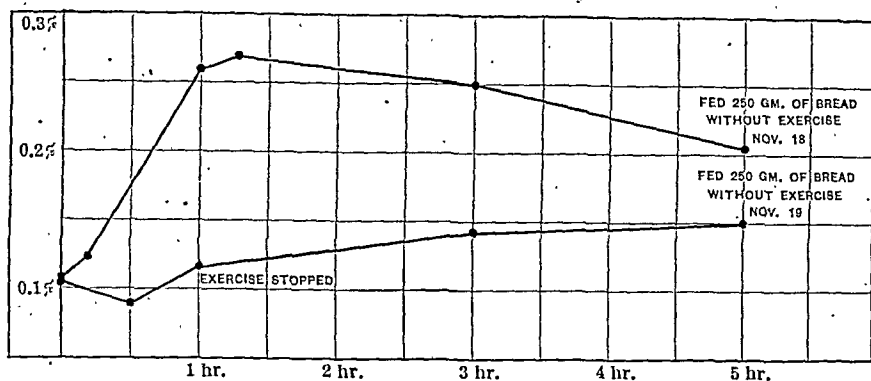


CHART II.—Dog B2-63. Weight 30 kgm. Mild diabetes.

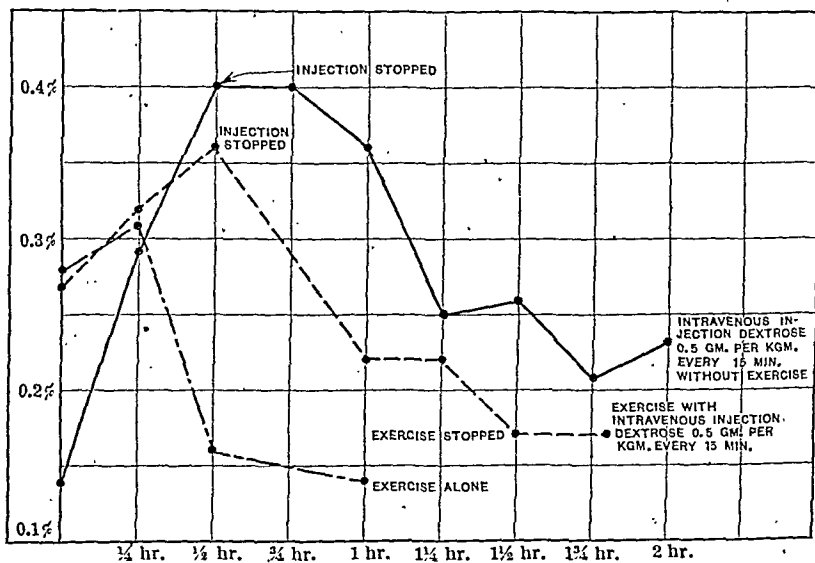


CHART III.—Dog B2-79. Mildly diabetic.

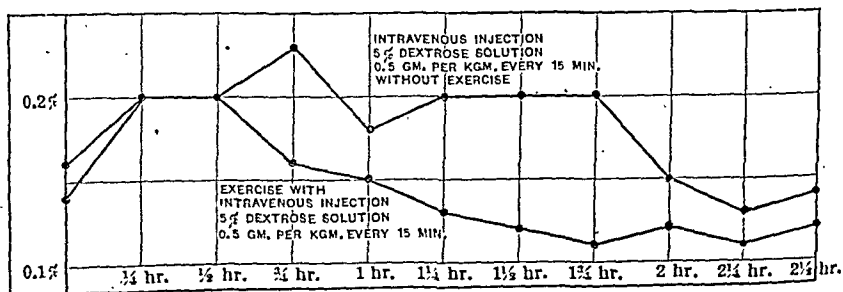


CHART IV.—Dog B2-88. Moderate diabetes.

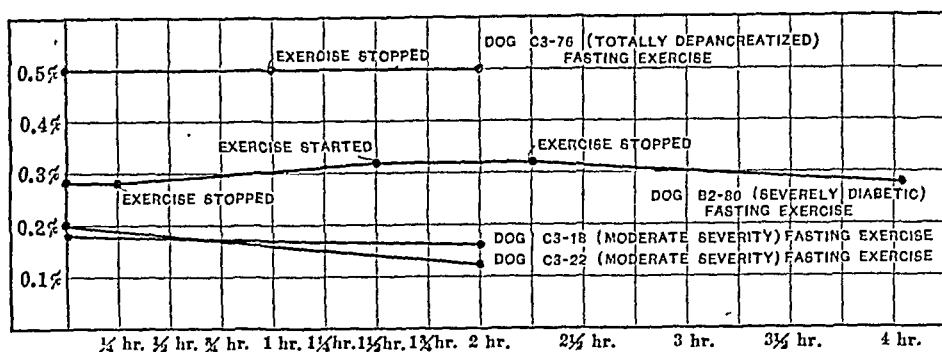


CHART V.—Exercise in severely diabetic dogs.

RETENTION OF PROTEIN DURING DIET REDUCTION TO RELIEVE THE GLYCOSURIA IN DIABETES MELLITUS.

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THERE was recently reported from this clinic a dietetic treatment of diabetes mellitus.¹

The procedure is essentially the maintenance of the protein intake at a moderate level, the restriction of the fat and the relatively rapid reduction of the carbohydrate until the patient's glycosuria disappears. The carbohydrate tolerance is then built up by a gradual increase in the carbohydrate intake (starvation days are dispensed with). The treatment is controlled by daily twenty-four-hour urine analyses and frequent blood analyses.

Some 15 cases were reported in the earlier paper. At the present writing 40 cases (63 admissions) have been treated under this method of protein retention in the diet.

The mortality was 5 per cent. (2 cases). One of these two was a case of carcinoma of the prostate gland, with retention of urine and a mass in the left lower abdomen; the patient died the second day postoperative. The other case was a refractory patient who had been in the hospital for three admissions. At no time would he follow the prescribed diet, and died of diphtheria and a lung abscess; pure culture of Klebs-Loeffler bacilli were obtained from the bronchi and abscess cavity at necropsy.

With the exception of one case, which showed a slight amount of acetone, all cases were sugar- and ketone-free upon discharge.

There is a gradual reduction in acetone and diacetic acid from the beginning of dietary treatment.

¹ Fenlon, R. L.: Diet Reduction with Retention of Protein to Relieve Glycosuria in Diabetes Mellitus, *Bost. Med. and Surg. Jour.*, February 12, 1920, No. 7, clxxxii, 168-171.

All but one of the cases coming under observation a second time have increased in weight.

This method of relieving glycosuria in diabetes mellitus and of subsequently establishing the dietary tolerance has been found applicable to patients of all ages.

General Outline of Treatment. Examination of the patient.

(a) When a case is admitted a careful history is taken by the medical intern in charge, special note being made as to the age of the patient, the duration of the symptoms and the severity of the disease, the complications, if any are present and the diet followed before entrance to the hospital.

(b) A complete physical examination.

(c) Routine blood and urine analyses are made, *i. e.*, blood sugar and fat; urine sugar acetone and diacetic acid.²

According to the data collected in the above-mentioned examination the treatment to be followed in the particular case is determined, and each case is classified a severe, moderate or mild type to facilitate its subsequent treatment.

The severe type includes all patients under twenty-one years of age, even though the diabetes may appear mild; all cases showing the three cardinal urinary findings acetone, diacetic acid and sugar; cases having a hyperglycemia accompanied by a hyperlipemia and those showing a tendency toward coma. Into the group of moderate diabetics fall all those showing sugar and acetone in the urine or having hyperglycemia, with slight or no hyperlipemia.

The mild type includes cases showing only sugar in the urine and having a hyperglycemia, with only slight or no hyperlipemia.

Method of Establishing a Carbohydrate Tolerance. While under treatment (after the glycosuria has been overcome) the amount of carbohydrate is raised each day, particular care being exercised to avoid the reappearance of sugar in the urine. In this series a "break" (glycosuria) occurred in 7.5 per cent. of the cases. The reason for avoiding a "break" is that a patient going out of the hospital without glycosuria appearing when the arbitrary carbohydrate tolerance is reached has a more stable outlook than one who is discharged with a weakened sugar function as shown by the recent "break."

It is evident that the most of these cases have been sent out on what might be termed an arbitrary carbohydrate tolerance; in other words, on a daily intake which is lower than the actual tolerance, a margin of safety is thus provided. The factors entering into the determination of this are the specific gravity of the urine, the severity of the case, the amount of urine passed in twenty-four hours and the hunger as expressed by the individual.

² Blood fat by Bloor's method. Blood sugar by Benedict Myers's method. Acetone by Rothera's Reaction. Diacetic acid by Gerhardt's method.

The specific gravity reading varies in each case at the time the patient is sugar-free. As the dietary treatment progresses the specific gravity generally decreases somewhat below this point. As the carbohydrate intake increases toward the arbitrary tolerance the specific gravity gradually approaches the level of the first sugar-free reading. In most cases it is not advisable to further increase the carbohydrate intake after the specific gravity reading rises to this level.

The severity of the disease as shown by the urinary and blood findings at the onset of the treatment and deductions drawn from the individual case give an approximate knowledge of the patient's tolerance.

The daily amount of urine passed also is an indication to a slight extent. As an example, when the succeeding daily amounts fluctuate markedly in the following manner, 1200 c.c., 2100 c.c., 1150 c.c., 1900 c.c. it is well to be cautious with the carbohydrate increase.

The final and most important point is the hunger of the patient. It is not advisable to raise the diet in carbohydrate when the patient maintains that his food intake is sufficient. No definite caloric intake (according to the weight of the individual) is followed in the treatment at this hospital. The final diet is adjusted to suit the wants of the patient. In a very few cases the diet was increased after the hunger was satisfied and glycosuria resulted.

Fehling's test for sugar in the urine as used here follows: Equal amounts of "A" and "B" solutions are mixed in a test-tube (2 or 3 c.c. of each) and boiled in a water-bath. One c.c. of urine is added and the boiling continued. There may be no direct reduction when hot, but the reduction may appear when the tube and contents are set aside to cool.

Dietary Treatment Used to Relieve Glycosuria in Severe Cases. In cases six or seven years old 35 to 40 grams of protein per day are given, the amount being increased with the age and size of the patient. An adult receives 70 to 80 grams per day. This protein level is maintained throughout the patient's stay at the hospital unless a higher caloric diet is desired upon discharge; at that time the protein allowance may be increased.

h. Fat is eliminated from the diet on the day of admission and is the last constituent to be replaced.

The daily carbohydrate intake in these cases is placed at from 130 to 140 grams and is maintained at this level for two or three days.

Accessory treatment at the onset consists in bed-rest, retention of body heat with blankets, forced warm drinks (fat-free broths, weak tea or coffee and warm water). The rate of forcing these fluids depends upon the amount of urine eliminated in twenty-four hours, the object being to keep the fluid intake at a level slightly greater than or equal to the fluid output.

To summarize: The protein is kept at a constant relatively high

level (35 to 40 grams in children, 70 to 80 grams in adults), the fat is practically eliminated and the carbohydrate is at 130 to 140 grams. The next step in the diet reduction is the diminution of the carbohydrate 10 or 15 grams a day until the patient's glycosuria is relieved. If the glycosuria does not disappear when but 10 grams of carbohydrate per day are given the treatment as outlined in a previous paper is followed.³

"Third Step. If glycosuria is still present add 50 to 100 grams of oatmeal to the diet for two days.

"Fourth Step. If glycosuria persists, repeat the diet used just preceding the oatmeal days, lowering the proteins one-third. Keep the patient two days on this diet if necessary.

"Fifth Step. If not aglycosuric, starve, giving only fat-free broths and water for a two-day period.

"Sixth Step. If necessary revert to the oatmeal diet for two days and again starve."

During the period of low caloric intake the calories may be increased by the use of alcohol. Alcohol (as whisky) has not interfered in any way with the establishment of a sugar tolerance in this series of cases.

When the patient becomes aglycosuric (at which time he is generally diacetic acid-free and showing less acetone in the urine) the carbohydrate is increased 1 gram per day in the young or 3 grams per day in adults. The fat is gradually increased when the carbohydrate totals 18 to 20 grams, but is kept at least 10 grams lower than the carbohydrate until the laboratory tests indicate that the carbohydrate tolerance has been reached. The fat at that time may be gradually raised to the same level as the protein or even 5 grams higher. The allowance of fat in the final diet is checked by a blood fat. The patient is then instructed to return to his home for a period of two or three months since this diet, as a rule, provides sufficient calories for the time being and will give a rest to the metabolic mechanism.

At the end of this time a return to the hospital is advised when a readjustment of the diet is made, the amount of carbohydrate being increased and the fat or protein changed if necessary.

The long period of diet reduction in this type of diabetes is invaluable for overcoming the hyperlipemia. One case treated as outlined above came in with a blood fat of 1.14 per cent. and was discharged with a blood fat of 0.596 per cent. A second case upon admission showed 2.28 per cent. blood fat; three weeks later 1.14 per cent., a reduction of $\frac{11}{18}$ of the hyperlipemia was noted, and upon discharge the blood fat had been reduced to 0.91 per cent. Other cases with less marked hyperlipemia had a normal blood fat upon discharge. These cases all had negative urines upon discharge, *i. e.*, neither sugar, acetone nor diacetic acid was present.

³ Loc. cit.

Case History and Chart of Mr. F. L. Clinical Number, 7230.

Complaints. Excessive urination and weakness of the calves and wrists.

Social History. White male, aged fifty years; farmer. No venereal history.

Family History. Negative.

Past Medical History. Digestive system: Has always had a very good appetite. His wife often said that he ate too much. Always drank lots of water. Occasionally some belching and heartburn. Otherwise negative.

Present Illness. Began about May, 1919, with nocturnal frequency and excessive twenty-four-hour urine. The urine looked like salt water. Had to void five or six times at night. He could eat like a trooper. Had difficulty in satisfying his thirst, went to a physician and was diagnosed diabetes. Later went to another physician who made the same diagnosis and placed the patient on a diet of eggs, fish, meats and fats, but no sweets. Advised the patient to eat fats and to drink cream. Could not follow this diet longer than six months. Began to be a little deaf nine months ago and has had trouble with vision. At present complains of weakness in the calves of the legs and wrists and excessive urination. Best weight, 180 pounds. Present weight, 147 pounds.

Day.	Sugar.		Acetone.	Diacetic acid.	Protein	Fat.	Carbo-hydrate.
	Per cent.	Gm.					
1	6.0	178	++++	+++	82	8	123
2	5.1	132	+++	++	84	7	141
3	6.0	175	+++	++	80	5	133
4	5.4	142	+++	++	88	19	110
5	5.7	166	++	++	90	15	100
6	5.4	122	++	++	85.	12	88
7	5.4	143	++	+	85	8	81
8	5.1	109	++	+	85	8	70
9	3.3	101	++	+	85	10	58
10	2.0	73	++	tr.	85	13	50
11	1.9	77	++	tr.	82	19	40
12	1.3	57	++	s. tr.	85	8	31
13	1.0	44	+	v. s. tr.	85	8	27
14	0.7	22	tr.	v. s. tr.	80	7	21
15*	0.2	6	s. tr.	v. s. tr.	84	7	16
16	0.5	28	s. tr.	v. s. tr.	86	6	14
17	0.4	24	s. tr.	v. s. tr.	80	6	15
18	0.2	11	s. tr.	v. s. tr.	83	10	9
19	0	0	v. s. tr.	0	81	6	8
20	0	0	v. s. tr.	0	80	7	10
21	0	0	v. s. tr.	0	83	9	12
22	0	0	0	0	83	8	15

* 4 P.M. urine specimen was sugar-free. Sugar (by mistake) was served with evening meal.

Tr. = trace. S. tr. = slight trace. V. s. tr. = very slight trace.

Blood on first day = sugar, 0.454 per cent.; fat, 2.28 per cent.

Physical Examination. Mucosa of mouth and throat is red and dry. Tongue is dry and fissured. Acetone odor to breath. Skin dry and desquamating. Muscles everywhere atrophied and show myoidema. Otherwise negative.

Laboratory Findings. Serum Wassermann negative.

Urine examination: Specific gravity, 1038. Sugar, 6 per cent. Acetone, + + + +.

Diacetic, + + + (blue-black).

Blood: Sugar, 0.454 per cent.; fat, 2.28 per cent.

Blood count normal.

Patient was seen again six weeks after discharge, active in farm work and had gained 12 pounds in weight.

The Treatment Followed in the Moderate Type of Diabetes. 80 to 90 grams of protein are given. This amount is not changed except just before discharge, when it may be increased if so desired; 12 to 15 grams of fat daily are allowed in order that the diet may be more palatable. The same amount of carbohydrate as protein is included in the diet. As an example the diet at the beginning of the treatment will be 90 grams protein, 15 grams fat and 90 grams of carbohydrate.

The carbohydrate is then reduced 15 to 20 grams daily until the urine is sugar-free. The carbohydrate is then increased 5 to 8 grams daily until the tolerance is reached. When the diet contains 50 grams or more of carbohydrate the fat is increased 10 to 15 grams per day until the total amount is not more than 10 grams above the next highest constituent (either protein or carbohydrate).

The treatment is varied as follows in cases with nephritis: In adult cases with nephritis the protein is kept at 60 grams daily. The reduction of the carbohydrate from 90 to 100 grams is made slowly, *i. e.*, 10 grams daily, until the patient is aglycosuric. Fat and carbohydrate are increased as above.

Two cases of diabetes and nephritis associated with gangrene have been treated in this series, and in both instances the gangrene cleared up before the patient's discharge from the hospital.

Treatment Followed in Mild Type. Protein and the carbohydrate are placed at 100 grams daily; fat at 20 to 30 grams.

The carbohydrate is halved daily until the urine is sugar-free and is then increased 10 grams per day until the tolerance is reached. When the carbohydrate reaches 60 grams the fat is added 25 to 30 grams daily until the total amount is not over 15 grams higher than the next highest constituent of the diet.

Case History of Mr. O. L. Clinical number, 6999.

Entrance Complaint. Poor vision and inability to hold his urine.

Social History. White male, aged sixty-two years farmer. No venereal history.

Family History. Negative.

Past Medical History. Malaria at age of twelve years. Typhoid at thirty-six. Thirty-two boils on the back of his neck and in his

hair three years ago. Swelling of the ankles during the day for the past two years. Good deal of cramping of the muscles of the legs and thighs the past seven or eight years. Appetite always very good. For the past twelve years has had spells of excessive thirst, and has never missed getting up from two to six times to urinate at night. Often wets his clothes. Poor sleeper the past five or six years. Has been seeing double lately. Has staggered a little, assigned to weakness of the legs.

Present Illness. Inability to hold urine began about twelve years ago and was gradual in its development. Worse at times, especially when he would get thirsty and drink a lot of water. Would have to get up at night to urinate and passed one to two gallons of urine in twenty-four hours. Appetite always good, but has had a special craving for sweets. Often noticed that bees would gather and apparently feed on his urine. For the first three years he used bran bread, and this seemed to help a good deal. Sugar was found in the urine and the patient told that he had diabetes. Has eaten nothing that he knew contained starch or sweets for the past twelve years, excepting pies; he, however, uses sugar in tea and coffee. Always had a preference for fat meat. Noticed that he was getting weaker about two years ago. Skin is dry but never itched. In July, 1919, the patient's vision began to fail. Saw double. Seemed to have a smoky scum over the left eye and could only see with this eye when he looked sideways. Weighed 270 pounds when thirty years old. Maintained about the same weight until he was forty. Lost weight up to fifty (onset of present illness). Present weight, 212 pounds.

Physical Examination. Arcus senilis marked in both eyes. Pupils react to light and accommodation. Left pupil slightly oval in shape. Definite Romberg test. Misses heel to knee test. Walks with a wide base. Ataxic. Knee-kicks and tendo achillis only present on reinforcement. Bilateral neuritis of the nervus cochlearis. Diabetic retinitis.

CHART OF TREATMENT OF MR. O. L.

Day.	Sugar.		Ace-tone.	Diacetic acid.	Blood.		Protein.	Fat.	Carbo-hydrate.	Calo-ries.
	Per cent.	Gram.			Sugar.	Fat.				
1	2.2	20	0	0	0.263	0.857	94	6	105	850
2	1.1	13	0	0	94	8	90	808
3	0.0	0	0	0	90	16	47	692
4	0.0	0	0	0	94	12	36	628
5	0.0	0	0	0	93	23	62	827
6	0.0	0	0	0	97	31	75	967
7	0.0	0	0	0	98	43	84	1155
8	0.0	0	0	0	98	66	80	1306
9	0.0	0	0	0	96	88	90	1536
10	0.0	0	0	0	98	108	100	1764
11	0.0	0	0	0	0.133	0.732	100	110	100	1790

Laboratory Findings. Blood count was negative except for an eosinophilia of 3 per cent. Serum Wassermann negative on two tests.

Weekly Fast Days. Weekly fast days do not enter into the treatment used either at the University Hospital or that subsequently followed by the patients in their homes.

The purpose of this treatment is to produce as stable a carbohydrate metabolism as possible. This is done by establishing the tolerance with small increments, 1 to 2 grams per day in all severe cases. In our opinion weekly fast days may defeat this purpose, in that the withdrawal of the carbohydrate and the rapid resumption of the load may tend to strain the sugar mechanism. Out of 38 cases so treated 8 have returned for an increase of the carbohydrate in the diet. None of these 8 cases have shown glycosuria while at home for periods of three to five months and the tolerance of all upon return has been set at a higher level.

Cases are advised to return to the hospital should they desire an increase in their diet; however, they are asked not to return in less than two months unless something untoward develops.

CHART OF RETURN CASES

Case.	Diet first discharge.				Diet second discharge.				Diet third discharge.			
	Pro.	Fat.	Cho.	Cal.	Pro.	Fat.	Cho.	Cal.	Pro.	Fat.	Cho.	Cal.
1	60	90	50	1250	85	85	75	1405	85	85	85	1445
2	65	75	45	1115	60	75	75	1215				
3	90	90	40	1330	100	100	80	1620				
4	40	35	31	600	70	70	50	1110				
5	70	90*	60	1330	100	115	85	1775				
6	100	100	85	1640	110	120	105	1940				
7	100	110	100	1790	100	100	115	1760				

* Discharged under previous method of treatment.

Case 1. Nineteen years old, slightly under weight. During first admission she "broke" on 40 gm. of carbohydrate.

Case 2. Slight build, no complaint of hunger.

Case 3. Tall, slender, "broke" on 46 gm. of carbohydrate (first admission).

Case 4. Boy, aged six years. Has gained in weight and plays with other children.

Case 5. Travelling man, aged thirty-three years.

Case 6. Male, aged twenty years. Plays basket ball on a town team, trapped and hunted between his two admissions and gained ten pounds in weight.

Case 7. See case report No. 6999.

Results from High Fat Diets. Some cases before entrance to the hospital had lived upon a diet rich in fats. The difficulties encountered while treating such cases suggested the following conclusions:

1. A longer period of time with a continuous low calorie diet was necessary to overcome the glycosuria and ketonuria.

2. Although the tendency of a high fat diet (especially with a low carbohydrate intake) to produce acidosis is well known; too little attention is paid to this point by the general practitioner. Many patients are advised by their physician to limit their sugar, bread, potato and starch intake, but no mention is made of the fat intake; in fact a few cases (see case report of Mr. F. L.) have been told to increase their fat consumption by eating cheese, butter, nuts, etc., and drinking cream.

3. High fat diets appear to cause a decrease in the carbohydrate tolerance; that is, with long-continued, high fat ingestion the carbohydrate seemingly cannot be placed at as high a level as the case should tolerate.

Foci of Infection. Demonstrable foci of infection such as diseased teeth, tonsils, etc. are removed during the patient's stay in the hospital, the diet being established before operation. The daily food intake (that is only the fat and carbohydrate) is reduced on the day of the operation and replaced slowly as the urinary picture clears.

Oatmeal Treatment. Oatmeal, because of its slow absorption and high potassium content, has been used recently in a few instances as the principal carbohydrate of the food intake during the diet reduction. Two-thirds of the daily carbohydrate is given as oatmeal. Results in a case follow: The first urine specimen received from this patient contained 12.5 per cent. of sugar. The urine was sugar-free after four days of diet reduction. Treatment was completed in sixteen days and then his tolerance was set at 100 grams of protein, 100 grams of fat and 75 grams of carbohydrate.

Case History of Mr. M. G. Clinical Number 7598.

Entrance Complaint. Diabetes.

Social History. White male, aged twenty years; single; farmer. No venereal history.

Family History. Negative.

Past Medical History. Light attack of influenza in the fall of 1918.

Present Illness. Began about five weeks ago with polyuria, which gradually increased until in two weeks he was passing thirteen pints of urine in twenty-four hours. He developed a ravenous appetite and drank large quantities of water. Two weeks before admission he consulted a physician, who found sugar in his urine. The diet recommended was to omit sugars and syrups and to reduce bread and potatoes to half the usual amount. After this the total twenty-four-hour urine decreased to an average of seven to nine pints. Weight two months ago was 158 pounds and at present 138 pounds. He has felt drowsy in the daytime during the past two weeks.

Physical Examination. Patient is a slender, fairly well-nourished, white male of twenty. Face is flushed. Skin on the body is dry. Tongue is semi-moist. Otherwise negative.

Laboratory Findings. Serum Wassermann negative on two tests. Blood count was negative except for an eosinophilia of 5 per cent. Urine: Specific gravity, 1052. Sugar, 12.5 per cent. Acetone and diacetic negative. Blood sugar, 0.270 per cent.

Some Dietary Regulations Which Are Deemed Advisable to Incorporate in the Treatment. 1. Milk and orange are to be excluded from the diet in severe cases. Milk because of its prompt assimilation is given only when the carbohydrate tolerance is above 30 grams; exception to this is made in cases of children. Orange tends to cause a glycosuria before the normal tolerance of the particular case is reached. In a few instances the feeding of orange caused a glycosuria which upon withdrawal of orange from the food was relieved and the carbohydrate was increased to a higher level without the reappearance of sugar in the urine. Grapefruit and rhubarb are used in the place of orange without the danger of causing glycosuria prematurely.

2. No cane sugar is to be given as such, regardless of the tolerance. Saccharin is to be used for sweetening.

3. The food is to be divided equally among the three meals of the day, *i. e.*, one-third of the protein, one-third of the fat and one-third of the carbohydrate are to be included in the breakfast, in the dinner and in the supper.

4. Bananas are not to be included in the diet when the tolerance, is less than 90 grams of carbohydrate.

Instructions Given to the Patient for His Use after Leaving the Hospital. While the patient is in the hospital he receives a course of instructions on his diet in which he becomes familiar with the food constituents, protein, fat and carbohydrate, both as to the physiologic action, source and calorific value.⁴

After the patient has become familiar with the food value of most of the common food materials, he is taught to calculate a day's diet. Great stress is put upon the equal division of the food among the three meals of the day, *i. e.*, one-third of the protein, one-third of the fat and one-third of the carbohydrate at each meal.

Six days' diet are given to the patient when he leaves, and he is instructed to live only on a weighed diet. Since one-third of his food allowance for the day is given in each meal there can be a variety of the day's diets; for a breakfast of one day and a dinner of another and a supper of a third day can be taken with no danger of exceeding his tolerance. The patient is taught to substitute one food for another, so that he may vary his diet as the foods in season vary, and he is more content to live on a prescribed diet too when he can make slight changes to suit his individual taste. In order that no difficulty may arise in regard to the use of a balance for weighing the food, he is taught to weigh out foods on the balance that he is to use

⁴ Government Bulletin No. 28, Chemical Composition of American Food Products has been found helpful.

after leaving the hospital. This instruction enables the patient to calculate his own diet if he so desires.

The doctor in charge gives the patient instructions in the qualitative urine tests for sugar and diacetic acid, and the patient is instructed to test the urine for sugar each day. He is told to use but 1 c.c. of urine in performing Fehling's test and is shown the various phases of reductions with this test when sugar is present, green, yellow and red. Instruction is given to reduce the carbohydrate of the diet slightly when a green or yellow reaction results, and when the urine is again sugar-free to gradually return to the former level. He is instructed to return to the hospital if the reduction is persistently red. In case of an infection such as a severe cold, tonsillitis or other condition with increased temperature, the patient is advised to test his urine for the presence of diacetic acid with the ferric chloride solution, and if he finds the test to be positive to reduce the fat in his diet until the diacetic disappears, when he may gradually increase the fat until the former amount is being taken.

THE BACTERIOLOGY OF THE FASTING STOMACH AND DUODENUM: AN EXPERIMENTAL STUDY BASED ON THE FINDINGS IN THIRTY DOGS.

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CHICAGO, ILL.

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CLINICALLY it has long been recognized that the upper portion of the gastro-intestinal canal contains relatively few pathogenic bacteria. Cushing and Livingood¹ found difficulty in recovering microorganisms from the mucous membrane of the stomach, duodenum and even the jejunum as far down as complete emptying of the canal occurred. Kohlbrügge² in discussing the autosterilization of the intestinal canal stated that the small bowel either has no bacteria at all or, when it does show them, that they belong to the colon group. On the other hand, as long ago as 1886, Escherich³ showed that in infants *B. coli* predominates in the lower portion of the intestinal canal while *Bacillus lactis aërogenes* is found higher up. Gilbert and Dominici⁴ examined the intestinal contents of dogs which were killed three hours after a meal of bread and meat. They found many organisms in the stomach, few in the duodenum and a gradually increasing number down the small bowel. Kendall⁵ Hess,⁶ Sisson,⁷ Torrey⁸ and others have obtained similar results.

Various factors enter into the production of this relative "amicrobism" of the upper intestinal tract. The foremost of these is perhaps the bactericidal action of the gastric juice. In 1890, Miller⁹ took gastric contents three hours after a meal and incubated it. He found three kinds of bacteria three hours afterward, one kind ten later and none at the end of fourteen hours. Gillespie¹⁰ also has shown that there is a marked decrease in the number of bacteria during the period of digestion.

Many experiments have been made to determine which constituent, or combination of constituents, of the gastric juice is the germicidal factor. Macfayden¹¹ estimated the maximum antiseptic power of hydrochloric acid by means of gelatin plate cultures. He added known quantities of the acid to the gelatin, but did not determine the percentage of free acid remaining after sterilization. Working with a number of organisms, including *Staphylococcus aureus*, *Bacillus pyocyaneus*, *Bacillus anthracis* and *Bacillus typhosus*, he found that pepsin alone had no effect. Hydrochloric acid either alone or along with pepsin hindered the growth of all the organisms, its action not being modified by the presence of pepsin. *Staphylococcus aureus* and *Bacillus typhosus* were killed by 0.3 per cent., *Bacillus anthracis* by 0.1 per cent. and *Bacillus pyocyaneus* by 0.02 per cent.

That organisms do not all show the same resistance to acid, and that combined acid is less bactericidal than free was shown by Gillespie,¹⁰ who attempted to reproduce the conditions present during normal digestion, particularly by adding the acid in a manner similar to that in which it is added during life. He found that with a total acidity of 0.306 to 0.414 and a free acidity of 0.0935 per cent., *Staphylococcus aureus* was killed in two to three hours; whereas with a combined acidity of 0.684 per cent. the organism multiplied. *Bacillus coli* was killed in from one to two and a half hours in acidity ranging from 0.234 to 0.511 per cent., part of it being free hydrochloric acid. Fermi¹² added various acids and alkalies to sterilized neutral glycerine agar and obtained results slightly higher than those obtained by Gillespie. In 1915, Broadhurst¹³ found that streptococci survived 0.2 to 0.4 per cent. hydrochloric acid for ten to seventy minutes. Recently, Davis¹⁴ found that "gastric juice of normal acidity from man and from rabbits kills hemolytic streptococci in two to five minutes," and that "gastric juice in achylia may not kill them for several hours." He also found that when introduced into the stomach of rabbits in large numbers virulent hemolytic streptococci occasionally pass through and appear in the feces. Further experiments in which the relation of the hydrogen ion concentration to the number and variety of organisms in the gastric contents is determined should be made.

That there is ample opportunity for some organisms to pass unharmed through the stomach is readily seen when one considers the following facts: (1) The acidity does not reach its maximum

until one-half to one and a half hours after digestion begins; (2) liquid food leaves the stomach almost immediately; (3) saliva laden with organisms is swallowed in interdigestive periods; (4) food particles may protect organisms from the action of acid, and finally (5) many bacteria, some of which are pathogenic, as, for example, staphylococci, *Bacillus coli* and *Bacillus typhosus* are resistant to a degree of acidity greater than found in the normal stomach during digestion. Cushing and Livingood¹ maintain there is a tendency on the part of the stomach to completely free itself together with the end-products of digestion from even those micro-organisms which are resistant to the gastric juice. In four cases of gastrostomy for stricture of the esophagus where no food had been taken for at least six hours the stomachs were found sterile at operation.

Gilbert and Dominici⁴ showed that a sudden reduction in the number of bacteria as the duodenum is reached occurs even during digestion. At one time bile and pancreatic juice were believed to have a bactericidal action, but the experiments of Leubuscher¹⁵ and others have shown that this is very slight if present at all. Yeasts alone are inhibited by bile according to Leubuscher. The dilution of the chyme may be a factor, as pointed out by Gilbert and Dominici. Hess⁶ found that a greater or less amount of bile in the duodenum stood in no definite relationship to the number of bacteria present. Cushing and Livingood¹ report a case of complete common duct obstruction, due to carcinoma, in which the duodenum was sterile after six hours' fasting, showing that "amicrobism" of this organ could occur without as well as with the presence of bile.

Duodenal contents have been variously studied in an attempt to establish a definite flora. Gessner¹⁶ examined the duodenal contents of eighteen persons shortly after death and found eight varieties. *Bacillus lactis aërogenes*, streptococci, *Bacillus coli* and staphylococci were among those found frequently and in considerable numbers. Hess⁶ catheterized the duodenum in infants a few hours old and nurslings from one to six weeks of age. A few organisms, mostly staphylococci and moulds, were found in the infants. Up to one week of age the most frequent organisms in the stomach and duodenum were staphylococci. *Bacillus coli* was found in the duodenum in only one instance. In children two to six weeks old *Bacillus coli* were almost invariably obtained from the duodenum and less constantly from the stomach. The samples were taken at a time when the stomach was relatively empty. The flora of the stomach and duodenum was found to be practically the same; only fewer organisms were obtained from the duodenum. Cushing and Livingood found many duodenums sterile after a period of fasting, and believe, therefore, that one should not speak of a definite flora of the duodenum. Sisson⁷ examined the bacterial content of the bowel at various levels in puppies fasted from eight to twenty hours. In each instance he obtained a reduction in the number of bacteria

in proportion to the length of the period of fasting, but in no instance was the duodenum sterile. Staphylococci, streptococci and *Bacillus coli* were the organisms most frequently encountered.

It was early recognized that the number of organisms at any level depends not only upon the period of fasting but also upon the type of diet. The following table is quoted from Gilbert and Dominici¹⁷ and contrasts the difference in number of bacteria between a mixed and a milk diet. His dogs were kept on milk exclusively for two weeks:

	Mixed diet.	Milk diet,
Stomach	50,000	100 organisms per mg.
Duodenum	30,000	50 " "
Ileum	100,000	1300 " "
Large intestine	30,000	1275 " "

The type of diet appears not only to influence the number of bacteria but also to exert a marked influence upon the varieties present. Kendall⁵ has shown that on a carbohydrate diet fermentative bacteria replace the proteolytic type—longer, thinner, Gram-positive rods replace the rather stout bacilli seen upon a protein diet. Torrey⁸ kept dogs on a regulated diet for a period of seven weeks and examined the intestinal contents at various levels eighteen to twenty hours after the last feeding. On a rice and meat diet a few streptococci and *Bacillus welchii* were found in the duodenum. When lactose was substituted for rice numerous *Bacillus acidophili*, a few streptococci and some hydrogen sulphide-forming bacteria were found. Finally, when saccharose was the carbohydrate used a few *Bacilli welchii* and hydrogen sulphide-forming bacteria were noted. Although Sisson found the same types of organisms throughout the intestinal tract, Torrey, on the other hand, found different organisms at various levels, and points out that "generalizations in regard to the bacterial conditions in the upper levels based on the examination of fecal specimens should be made with caution."

While working with Dr. Gatewood upon the relative efficiency of various cholecystenterostomies, including cholecystogastrostomies, cholecystoduodenostomies and cholecystocolostomies, an opportunity presented itself for making a qualitative study of the flora of the stomachs and duodenums of normal fasting dogs.

Method. Dogs kept on a mixed diet of bread and meat were not fed for fourteen hours previous to the operation. Aseptic technic was used throughout. The opening into the stomach or bowel was made with a clean knife and some of the contents aspirated with a sterile pipette. In this way two to four drops of semiturbid fluid could be obtained. This was inoculated directly into 10 c.c. of 1 per cent. dextrose broth and incubated for eight to twelve hours. Subcultures were then made on blood agar plates, dextrose agar tubes, plain agar slants (anaërobic) and litmus milk. The preliminary period of incubation was decided upon after it was found that subcultures made immediately sometimes remained sterile;

whereas inoculation from the same broth tube after eight to twelve hours gave an abundant growth. After twenty-four to forty-eight hours colonies were picked from the blood agar plates and from the dextrose agar tube for further identification. *Bacillus coli* were identified by their morphology, Gram's stain and motility, as well as by their growth in the various media (1 per cent. dextrose, lactose and saccharose agar tubes, litmus milk, Dunham's peptone and potato).

Gram's stains were made of a number of direct smears, but in the stomach these usually revealed only yeasts, and a few if any bacteria. In the duodenum no organisms at all or only isolated ones could thus be demonstrated. This method was therefore abandoned and stains were made of the sediment in the twenty-four-hour dextrose broth tubes and from the growth on four day old anaërobic agar slants. His's capsule stain was made on organisms grown in milk when media reactions made this necessary. All media were +1 acid to phenolphthalein. For blood agar plates ten drops of human blood were added to 10 c.c. of agar. In two cases 2 c.c. of a twenty-four-hour broth culture of *Bacillus coli* from the duodenum was injected into the peritoneal cavity of a guinea-pig. In each instance death was produced in about twenty hours, the organism being isolated in pure culture from the heart's blood.

In the duodenum Gram-positive organisms not constant in morphology and innocuous to rabbits and guinea-pigs were noted. They sometimes resembled cocci, at other times bacilli, showed a tendency to be arranged in pairs and in cultural characteristics agreed with *Enterococcus proteiformis*.

STOMACH.

Dog No.	2	3	4	8	9	11	14	15	16	17	18	32	34	35	36	Total.
Number of hours fasting	14	14	14	14	14	14	14	14	14	14	14	20	14	22	22	
<i>Bacillus coli</i>	0	0	+	0	+	0	0	0	+	0	0	0	+	0	0	4
<i>Staphylococci</i>	+	+	+	<i>citreus</i> +	0	+	+	+	+	+	+	0	0	0	+	11
<i>Streptococci</i>	0	+	0	<i>aureus</i> +	0	0	+	<i>green</i> +	0	0	0	0	0	0	0	4
<i>Subtilis</i> group	0	0	0	+	0	0	0	+	+	0	+	+	+	+	+	8
Moulds	+	+	0	0	+	0	0	0	0	0	0	+	0	0	0	4

DUODENUM.

Dog No.	19	20	21	22	23	24	25	28	29	30	31	34	35	36	11	Total.
Number of hours fasting	14	14	14	14	14	14	14	14	14	14	14	14	22	22	14	
<i>Bacillus coli</i>	+	+	0	+	+	+	0	+	+	0	+	+	+	+	+	12
<i>Staphylococci</i>	+	+	+	0	+	+	0	0	0	0	0	+	+	+	0	3
<i>Streptococci</i>	0	0	0	+	0	0	0	0	0	<i>green</i> +	0	0	0	<i>aureus</i> +	+	4
<i>Subtilis</i> group	+	+	0	+	0	0	0	0	+	0	0	+	+	+	+	8
Moulds	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<i>Enterococci</i>	+	..	+	..	+	0	0	0	0	0	0	0

* Pure culture.

While the number of animals examined is not large the uniformity of results is rather striking. It will be seen that in the duodenum, *Bacillus coli* was found twelve times out of fifteen, after a period of fasting of fourteen to twenty-two hours; whereas in the stomach this organism was found only four out of fifteen times. On the other hand staphylococci, most frequently of the albus variety, were found in the stomach eleven out of fifteen times, and only three times in the duodenum.

Streptococci were found an equal number of times in the stomach and the duodenum. Hemolytic streptococci were not found. Organisms that produce hemolysis were not infrequent, some of the *Bacillus coli* producing a rather wide zone (4 or 5 mm. in diameter) in twenty-four hours. Two out of the four streptococci isolated produced methemoglobin. In one duodenum *Streptococcus viridans* was found in pure culture.

Although in some instances immediate plating gave sterile cultures, by the method employed in these experiments no stomach or duodenum was found amicrobic even after the dogs had been fasted twenty-two hours (two cases). This would seem contrary to the results of Cushing and Livingood, who found quite a few sterile duodenums. These authors, however, took only an ordinary loop-full of material and made immediate aërobic and anaërobic plates.

Practically all organisms were facultative anaërobes. Spore-formers in most instances belonged to the *Bacillus subtilis* group.

Summary. 1. By taking two to four drops of material from the fasting stomach and duodenums of dogs a variety of organisms was invariably found.

2. *Bacillus coli* was much more frequently found in the duodenum than in the stomach.

3. Non-hemolytic streptococci were rarely found in either stomach or duodenum and hemolytic streptococci not at all.

4. Staphylococci were found in eleven of fifteen stomachs and in but three of fifteen duodenums.

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LEUKEMIA: TYPE DIAGNOSIS BY OXYDASE METHOD OF BLOOD-STAINING.

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THERE are two types of leukemia, the lymphatic and myelogenous, the diagnosis of which is based on doubtful clinical and hematological grounds. It is said that in lymphatic leukemia the lymph glands are enlarged out of proportion to the spleen, while in splenomyelogenous leukemia the splenic enlargement is more prominent. This is only true in a certain number of cases. When judgment of type is based on such clinical data, disappointment will often be encountered, due to obtaining blood-findings, which disagree.

In late years more confidence has been placed on the examination of stained blood smear. This is a helpful means, but is uncertain, too, for there are many questions among observers in regard to differentiation between lymphocytes and myelocytes. The simple statement that the myelocytes are granular and the large lymphocytes non-granular is a good working foundation, but the difficulty is in the recognition of the granules by the ordinary methods of staining. There are, fortunately, some blood smears that stain beautifully by a good fresh Wright stain, and no hesitation is made in deciding which is a granular or non-granular cell. Leaving aside the remainder of the findings in a blood examination of leukemia the distinction between the large lymphocytes and myelocytes is of

greatest importance. In order to do this the best plan is to stain all blood smears from cases of leukemia by the oxydase method.

In the use of the oxydase method, alpha-naphthol and dimethyl-para-phenylendiamin are brought together in the presence of an oxidizing agent which is present in the leukocytes. An alkaline media is required. When this is done a rapid precipitation of indophenol blue occurs which produces blue granular staining of their protoplasm. The reaction is given by neutrophil, eosinophil and basophil leukocytes and by myelocytes in bone-marrow and leukemic blood. The reaction is not given by lymphocytes nor red blood cells. The method is as follows: Solutions required:

Solution A.		
95 per cent. alcohol	9 parts
Formaldehyde solution (40 per cent. gas)	1 part

Solution B.		
Alpha-naphthol (Merck's reagent)	1 gram
40 per cent. alcohol	100 c.c.
Hydrogen peroxide (Must be fresh.)	0.2 c.c.

Solution C.		
Pyronin	1 gram
Anilin	4 c.c.
40 per cent. alcohol	96 c.c.

Solution D.		
0.5 per cent. solution of methylene blue (Grubler's BX).		

Directions. The films should be fixed by covering with solution A. After two minutes this is washed off with water and film flooded with solution B. This is washed off and the film is allowed to remain in a dish of running water for fifteen minutes. It is then dried and stained for two minutes with solution C. This is washed off with water and solution D is poured on and allowed to remain for thirty to sixty seconds. After washing with water the slide is blotted and mounted in neutral balsam.

Results: All myeloid cells, polynuclear myelocytes, transitional and myeloblasts, will show blue granules, while lymphocytes and lymphoblasts will not.

Caution: Solution B deteriorates very rapidly and must be made up fresh.

A leukemia case, the physical findings of which were not conclusive, was carefully studied by three separate hematologists. A brief summary of the findings will be of interest, as it shows the different interpretations placed upon cells observed stained by different methods within short periods of time:

A child, aged six years, was first seen October 12, 1919, with chief complaint of weakness. Mucous membranes were pale, a petechial rash that later changed to purpuric spots and general glandular

enlargement was present, including the spleen. The blood findings were as follows:

Red blood cells	2,140,000 Per c.mm.
White blood cells	51,000 "
Hemoglobin	40.0 per cent.
250 cells were counted on a slide stained by the oxydase method with following results:	
Polymorphonuclears (neutro)	46.0 per cent.
Large lymphocytes	13.0 "
Small lymphocytes	4.0 "
Myelocytes (neutro)	31.0 "
Mast cells	6.0 "

Many nucleated red cells were seen, the larger number of megaloblastic type. Moderate achromia, polychromatophilia, poikilocytosis and anisocytosis were present.

The blood was examined in another laboratory a few days later which corroborated the diagnosis of myelogenous leukemia and reported the following findings:

Red blood cells	2,400,000 per c.mm.
White blood cells	48,000 "
Hemoglobin	48.0 per cent.
Polymorphonuclears (neutro)	59.4 "
Eosinophils	0.4 "
Large lymphocytes	2.8 "
Small lymphocytes	10.2 "
Transitionals	0.4 "
Myeloblasts	6.4 "
Myelocytes (neutro)	20.4 "

Achromia, anisocytosis, polychromatophilia and poikilocytosis was present.

Platelets normal. Six megaloblasts and five normoblasts were seen in making the count of 250 cells.

Three days later another laboratory made an examination of the blood and stained the smear by Wright's method and submitted a diagnosis of lymphatic type from the following findings:

Red blood cells	2,192,000 per cmm.
White blood cells	74,000 "
Hemoglobin	30.0 "
Polymorphonuclears (neutro)	50.0 per cent.
Large lymphocytes	27.0 "
Small lymphocytes	14.0 "
Transitionals	1.0 "
Myelocytes	8.0 "

Irregularities in form were noted with abnormal red cells.

In the last examination it will be noted that a diagnosis of lymphatic leukemia was made from the blood findings. This was based on the finding of myelocytes of vanishing quantity. It is probable the method of staining had a great deal to do with the failure to recognize more myelocytes, as the two previous examiners had found them present in sufficient quantity by the oxydase method to make a diagnosis of lymphatic type. There are fluctuations in blood pictures to be sure, and cases are reported in which one type

has changed to another. The information relative to the latter cases is very meager. Then there is the question of individual observation over which there is no control. It is hoped the evidence submitted will encourage the use of the oxydase method of staining the blood smear to ensure a more accurate distinction between large lymphocytes and myelocytes.

Conclusions. 1. The distinction between lymphocytes and myelocytes by granules in the protoplasm is uncertain by the average examiner with ordinary methods of blood-staining and is liable to render his percentage proportions of these two cells inaccurate. This will result in incorrect type diagnosis of leukemia.

2. The oxydase method of staining the blood smear will be of assistance in making the distinction.

3. A description of a satisfactory method is given.

4. Summarized blood-findings are given which illustrate a possible error in failure to recognize myelocytes by simple method of staining.

I wish to express my thanks to Dr. John Phillips for the opportunity of making examinations of case reported.

THE CURABILITY OF TUBERCULOUS MENINGITIS.

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It is now generally accepted that tuberculosis is a curable disease. The struggle against tuberculosis is based in large measure on the fact of its curability, the effort being to secure as favorable circumstances as possible for the infected in order to bring the process to a standstill and cure. Examples of the cure of tuberculosis are numerous even when the very many latent tuberculous foci, particularly in the lungs and lymph nodes, that are cured spontaneously, are disregarded. Thus tuberculosis of lymph nodes in most cases cures itself without giving rise to any clinical phenomena of note, and this occurs in the lymph nodes of the neck, the chest and the abdomen as well as elsewhere. This is also true of tuberculous processes in the skin, mucous membrane, bones and joints. At the postmortem table one may see complete recovery even of the most extensive and destructive forms of tuberculosis of the bones. At the same time such processes may remain latent and encapsulated, but not healed, through years and years, as, for instance, the case of latent tuberculous spondylitis of twenty years' standing that I observed.

The curability of pulmonary tuberculosis is the corner-stone on which rests all our efforts against tuberculosis with the expenditure

of millions for sanatoria and other means to secure recovery in the largest number of cases possible, and in spite of many disappointments there is today no doubt but that sanatoria are of great value both in prolonging life as well as in promoting the definitive cure of tuberculosis in numerous cases, to say nothing about the other important purposes of such institutions. At postmortem examinations there is frequently occasion for wonder at the extent and destruction of tuberculous lesions in the lung that nevertheless have healed; large cavities may form, the walls of which become cleared of caseous masses, and practically complete healing may take place even after years, with extensive scar formation.

Renal tuberculosis is also not incurable as thought at one time. The process may become arrested and encapsulated, with, it is true, practically total destruction of the affected kidney,¹ and sometimes this occurs quietly and in a latent manner. At other times a marked tendency to fibrous arrest and healing of renal tuberculosis is noted, and in a few cases I have observed healing of small local tuberculous processes affecting one or more papillæ with the adjacent lining of the pelvis, and in such cases there no doubt at one time was an active process with excretion of bacilli in the urine. Such a course may explain certain cases of urinary infection with demonstration repeatedly of tubercle bacilli in the urine, in which after renal extirpation it has not been possible to demonstrate any definite tuberculous focus, old or new in the kidney. Assuming that tubercle bacilli were present in the urine, such cases can hardly be explained without there having been present some small focus which has healed completely. While there is no question that renal tuberculosis may heal, this is also true in even greater degree in regard to secondary tuberculous infection of the ureters and bladder—when the passage of tubercle bacilli from the kidneys is stopped the lower localizations may heal rapidly.

Genital tuberculosis also stands in a different light than it did. For some time it has been known that tuberculous salpingitis often heals, whether latent or after having caused definite symptoms, and whether complicated with tuberculous peritonitis or not. Experience has shown that tuberculous epididymitis sometimes lasts for years, and that it even may heal by encapsulation with or without local surgical treatment. On this account radical surgical measures, such as removal of the affected parts, with connected structures, no longer is practised as much as it used to be.

Tuberculosis of serous membrane may heal apparently easily and rapidly. Thus a tuberculous pleuritis may disappear, any grave consequences being usually due to the simultaneous tuberculous process in the lung. That tuberculous peritonitis is curable

¹ Harbitz, F.: Can renal tuberculosis heal spontaneously? Norsk. Mag. F. Lægevidenskaben, 1913, p. 1469.

has been demonstrated, among others, by Winge and Borchgrevink in Norway.

There is, however, one tuberculous localization that still is regarded as hopeless, namely, tuberculous meningitis and tuberculosis in the central nervous system. The usual prognosis in such cases is that tuberculous meningitis results in death in a comparatively short time. The numerous cases in which this disease is the cause of death, especially in childhood, appear to justify this grave outlook. Nevertheless it may be well to review our ideas in regard to this form of tuberculosis. While the physician, as a rule, holds out no hope in this disease—*et immedicabile vitium*—there nevertheless are recorded in the literature several observations that indicate the curability of even tuberculosis of the meninges. Thus a number of French physicians, particularly pediatricians, seem to have been early impressed with this possibility. In 1858 Rilliet wrote about the healing of tuberculous meningitis. More recently Barbier and Gougelet² discuss this subject, and other observations are being published.

When choroidal tubercles came to be recognized by means of the ophthalmoscope the diagnosis of tuberculous meningitis became more certain. A still better means was furnished by lumbar puncture because it made it possible to demonstrate the presence of tubercle bacilli either directly or by inoculation of guinea-pigs, and after 1891, when this method was introduced, the reports of healed cases of tuberculous meningitis increased rapidly. In 1914 Bokay³ collected no less than 29 such cases, including 2 of his own, 1 in a boy, aged eleven years and the other in a boy aged two years, in which the diagnosis was established by demonstration of tubercle bacilli in the spinal fluid or by the inoculation of guinea-pigs. If we add 5 older cases in which the diagnosis was made by demonstration of tubercles in the choroid, and if we include certain later cases⁴ in which tubercle bacilli were demonstrated, the total number of cases of healed tuberculous meningitis, concerning the diagnosis of which there can be no question, becomes about 40. Then we have further the older, somewhat uncertain cases in which the diagnosis of tuberculous meningitis with recovery was made by experienced clinicians, and finally cases with recovery in which there subsequently developed acute recidivation and death, sometime months and even years afterward.

There would seem to be but little doubt that recovery may succeed tuberculosis of the meninges, but there may be a question whether there was in any of the cases tuberculous inflammation at the base of the brain with partly gelatinous, partly purulent

² Sem. méd., 1914.

³ Jahrbuch. d. Kinderheilk., 1914, 80.

⁴ Bacigalupo; München. med. Wchnschr., 1915, Reichmann and Rauch, *ibid.*, 1919.

exudate about the bloodvessels and nerves. In many of the cases with recovery the brain symptoms seem to have been comparatively slight, there being no paralysis of the cranial nerves or other signs of definite localization, and the process of recovery was so rapid that it hardly would be possible for serious defects to heal so smoothly and promptly. It is indeed noteworthy that such acute inflammation may subside so completely and rapidly, and it suggests that possibly meningeal tuberculosis occurs more frequently than suspected, perhaps with evenascent symptoms (meningismus, pseudomeningismus), but this, of course, is merely a hypothesis.

In connection with this matter it may be well to mention the so-called pseudo-tumors described in the literature and which in part are regarded as instances of tuberculous meningitis with recovery; the conditions included under this term are, as a rule, afebrile but with general and local signs of brain tumor, with, however, negative results when postmortem examination is made. In some cases it has been concluded that a tuberculous meningo-encephalitis was present (Oppenheim).

When we come to the anatomic observations that bear on this particular form of tuberculous meningitis, we find that Rilliet in 1853 described a case in a child, aged five and a half years, that was sick for three months with signs of tuberculous meningitis, but recovered; five and a half years later a new attack of meningitis developed with death, and at the postmortem examination there was found, besides the usual lesions of meningitis, firm caseous masses in the depths of a furrow in one of the hemispheres, with thick membranes, and this was interpreted as the remnants of the old "healed" meningitis. Barth⁵ reports an instance of tuberculous meningitis in a boy twelve years old who recovered after two weeks. He died twenty-five years later of tuberculosis and there was found a fibrous condition of the leptomeninges with fibrous nodules along the vessels, and these lesions were regarded as the results of the old process. Johann v. Bokai, in 1862, described a meningitis in a girl, aged four years, who recovered, but died three and a third months later of tuberculosis of the lung when there was found small, round, soft, yellow nodules in the meninges over the hemispheres and in the Sylvian fissures. The case reported by v. Leube, in 1889, is well known: recovery from meningitis and death long afterward when small thickenings in the meninges of the upper end of the cord and the medulla with calcified miliary nodules at the base and hyaline degeneration of the vessels. Janssen⁶ observed a man, aged nineteen years, who had typical symptoms of tuberculous meningitis but recovered in the course of about six weeks. Some three years afterward he died of pulmonary tuberculosis and in the meninges at the base as well as the convexity were found caseous,

⁵ Deutsch. med. Wehnschr., 1894.

⁶ Ibid., 1896.

yellowish-white masses and gray as well as yellow tubercles. Brooks and Gibson⁷ report the following case: A girl, about four years old, developed what seemed like tuberculous meningitis; tubercle bacilli were found in the spinal fluid; the symptoms, however, subsided gradually, but after about half a year death resulted from a non-tuberculous bronchopneumonia; in the meninges of the brain there was found fibrous changes with scattered fibrous tubercle-like nodules, but no exudate, the ventricles being considerably dilated. Microscopically only fibrous tissue without definite tubercle structure was found. The case is regarded as a tuberculous meningitis undergoing healing. There are a number of other observations, more or less reliable, to the effect that postmortem residues of an earlier tuberculous meningitis were present, but in some cases, though not by any means all, this interpretation is open to doubt. There seems little doubt then but that it is well established, even in the older literature, that tuberculous meningitis may heal with fibrous changes. There are, furthermore, a number of observations indicating that tuberculosis of the meninges may run a chronic course through many months, with peculiar anatomic features indicating a tendency to heal. Thus Busse⁸ describes this case: in a woman, aged thirty-seven years, who had presented symptoms of a meningitic nature for about eight months, with emaciation there was found in the pia flat nodules and retracted scars with tubercles and tubercle bacilli, there being much fibrous tissue but no caseation. Busse regarded this as a rare form of chronic tuberculosis with scar formation. Estramann⁹ reports the following case: A man, aged thirty-seven years, was sick for at least about a year, the symptoms being headache, vomiting, bilateral hemianopsia, etc. After death there was found an extensive fibrous meningitis at the base with fibrous tubercles without caseation and evidently quite chronic. There were also small calcified nodules in the membranes and an indurated tuberculosis in the lymph nodes as well as a chronic tuberculous skin lesion. The clinical picture resembled somewhat dystrophia adiposa genitalis, but the hypothesis was normal. Rossle¹⁰ describes a chronic tuberculous meningitis in a woman, aged thirty-seven years, sick for seventeen months with marked cerebral symptoms (headache, dizziness, vomiting, spasms, pupillary stasis, and finally chronic convulsions and coma); postmortem there was found at the base of the brain a caseofibrous tissue with conglomerate tubercles in the meninges and the cortex as well as in the choroid plexus, the lateral ventricle being dilated. There was also a chronic tuberculosis of the tracheal lymph nodes. While tubercle bacilli could not be found, which also is true as regards

⁷ Lancet, 1912.

⁸ Virchows Arch., 1896, p. 145.

⁹ Mittheil. a. Grenzgeb. d. Med. u. Chir., xxiii, 191.

¹⁰ Verhandl. d. d. path. Gesellsch., 1914, xvii, 557.

giant cells, the Wassermann reaction was altogether negative, and so Rossle concluded that it concerned a tuberculous process. It is a case of this sort that I wish to report because it bears directly on the question whether meningitis of this kind from time to time may undergo healing.

It concerns a man, aged thirty-two years, under the care of Professor Leegaard. Except for an attack of influenza, in November, 1918, he had been well until in February, 1919. The symptoms of influenza were headache, fever, dizziness, vomiting, etc., and these lasted about one week. The illness in February, 1919, began in about the same way; there was fever, headache, vomiting and hic-cough, but these symptoms, except the fever, persisted at the same time as choked disk developed. A little later diplopia, nystagmus, ptosis and facial paresis appeared, with rigidity of the extremities and positive Babinsky. He died July 16, 1919, having been more or less restless and disturbed mentally during the last few days, when ataxia and Romberg's symptom also appeared. After death tubercle bacilli were found in the spinal fluid after much search.

The autopsy showed enlarged lymph nodes in the neck, caseous such as along the trachea and in the hilus of the lungs and along the bronchi, some nodes being sclerotic and calcified. Typical tubercles as well as caseous and hyaline degeneration, together with fibrous changes, were found microscopically.

In the right pleura were a few flat and firm but caseous tubercles and in the lung there were scattered tuberculous infiltrations, with central caseation along the bronchi, most marked in the upper lobe and the left apex. The microscope showed tubercles in fibrous transformation.

In the liver, spleen and kidneys nothing special.

The mesentery contained numerous caseous and calcified nodes. There were no tuberculous intestinal ulcers.

The brain was greatly swollen and edematous, with broad gyri and small sulci. On the convexity grayish-white lines paralleled the vessels. Over the entire base the membranes were grayish-white and thick, but without any definite exudate, here and there being scattered small grayish-white, rather firm nodules. In the left Sylvian fossa was a firm, grayish-white nodule as large as a hemp-seed. On the surface of the cerebellum were flat, very firm nodules. There was a marked internal hydrocephalus, the choroid plexus seemed to be infiltrated and the walls of the ventricles seemed soft and granular, particularly in the fourth ventricle and in the anterior and external parts of the lateral ventricles. No changes in the interior of the brain.

Numerous sections were examined from various parts of the base and elsewhere. There were more or less distinct evidences of a previous tuberculous meningitis and encephalitis with numerous tubercles on the surface of the brain as well as in the interior of the

ventricles. There was no sign of any exudate anywhere, but some infiltration of the membrane with lymphocytes here and there, particularly at the bottom of the sulci and about the larger vessels. However, large stretches of the membranes, particularly over the convexity, were quite free from any infiltration, but tuberculous inflammation had passed into the superficial brain substance along the bloodvessels, causing infiltration of cells in masses as well as bands with formation of small tubercles, consisting almost entirely of epithelial and giant cells, there being only few lymphocytes, and necrosis or caseation was hardly ever seen, but often a fibrous change in concentric order about the tubercles. The tubercles seemed to be chronic, with a definite tendency to heal. The brain substance about the tubercle was affected but very little, being even not markedly edematous; large tubercles of epithelioid cells seemed as if simply pressed into the surface with but little inflammatory reaction in the neighborhood. The walls of the ventricles, however, showed distinct evidences of softening and reaction, there being numerous large tubercles not merely on the surface but also along the vessels and a considerable, sometimes nodular, appendymal proliferation with superficial softening. These changes were more marked in the third ventricle than in the lateral, and the floor of the fourth ventricle contained conglomerate tubercles, with destruction of groups of ganglion cells.

Sections of the spinal cord from the cervical, upper and lower dorsal and lumbar parts showed areas of lymphocytic infiltration in the leptomeninges, with here and there, particularly in the lumbar part, distinct tubercles, consisting mostly of epithelioid cells, situated either in the membrane or extending into the white substance. Some of the bloodvessels in the membrane about the infiltrations were thick and hyaline. There was some infiltration in the spinal nerves. There was also infiltration in the walls of the bloodvessels in the fissures as well as in the small branches that extended into the cord itself; besides infiltrations of lymphoid cells there was also distinct tubercle formation, and tubercles were found about the vessels of the anterior horn and particularly the small branches of the motor ganglion cells. Similar tubercles were found also in Clarke's columns in the posterior horns, and, as stated, in the white substance. There was no edema, no definite degeneration in the ganglion cells and no leukocytic infiltration about these tubercles, which seem to be in the process of healing.

This case is characterized by a certain definite chronicity, shown particularly by the absence of any exudative changes. That the process at one time was exudative is indicated by the presence of scar-like areas in the membranes and thickening with hyalinization of the walls of bloodvessels. It is noteworthy that the tubercles were fibrous and that there was so little reaction about them even when they were situated closely adjacent to large and important

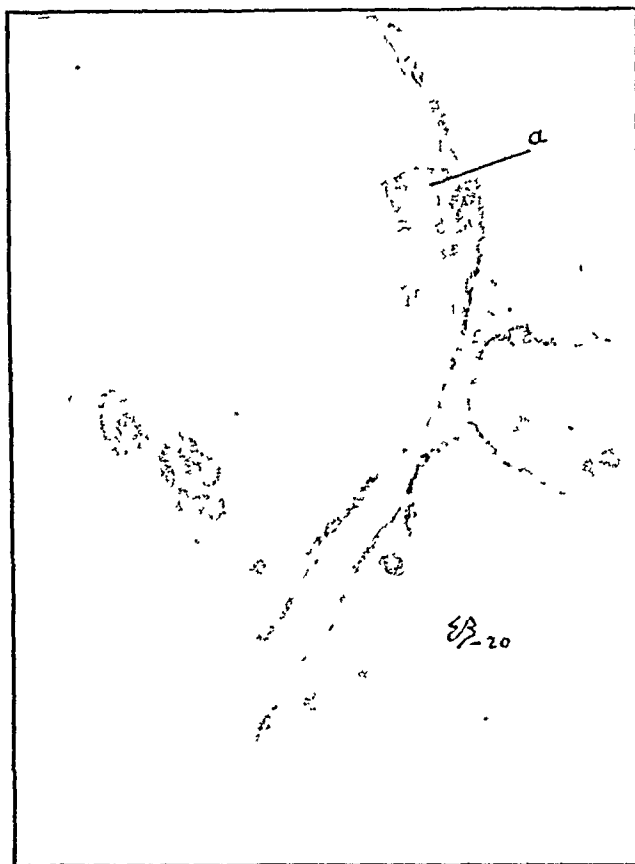


FIG. 1.—Section through Sylvian fissure. Lymphocytic infiltration in the meninges and tubercles in the surface of the brain. At *a* an infiltration of epithelioid cells extending into the brain.



FIG. 2.—Floor of fourth ventricle. Ependyma partly intact, floor nodular, numerous tubercles below the surface especially along vessels.

groups of ganglion cells. Nowhere was there any softening or degeneration of the tubercles. Mention should also be made again



FIG. 3.—Cervical cord. Tubercles in gray and white substance, infiltration of the membrane.

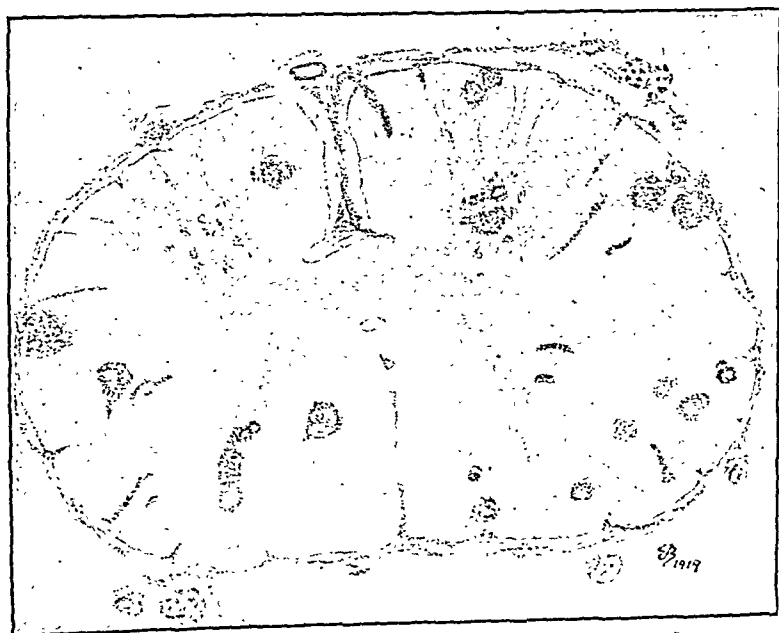


FIG. 4.—Lower part of dorsal cord with numerous tubercles along the vessels.

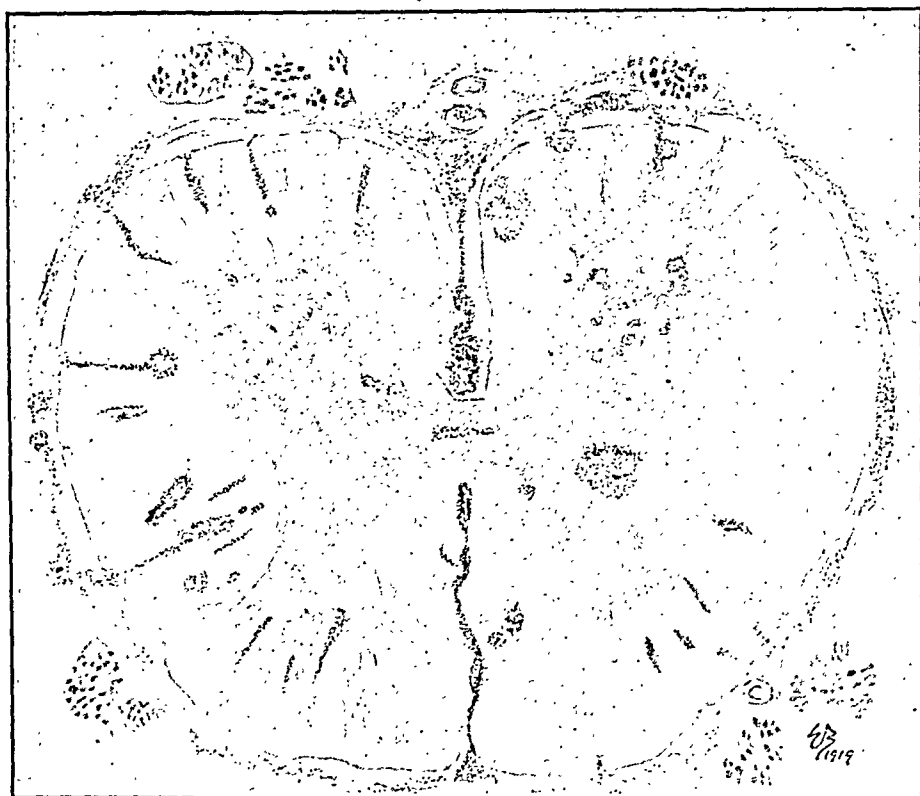


FIG. 5.—The lumbar cord. Infiltrations and tubercles in the membranes, especially in the fissures, as well as along the vessels in the white and gray substance.

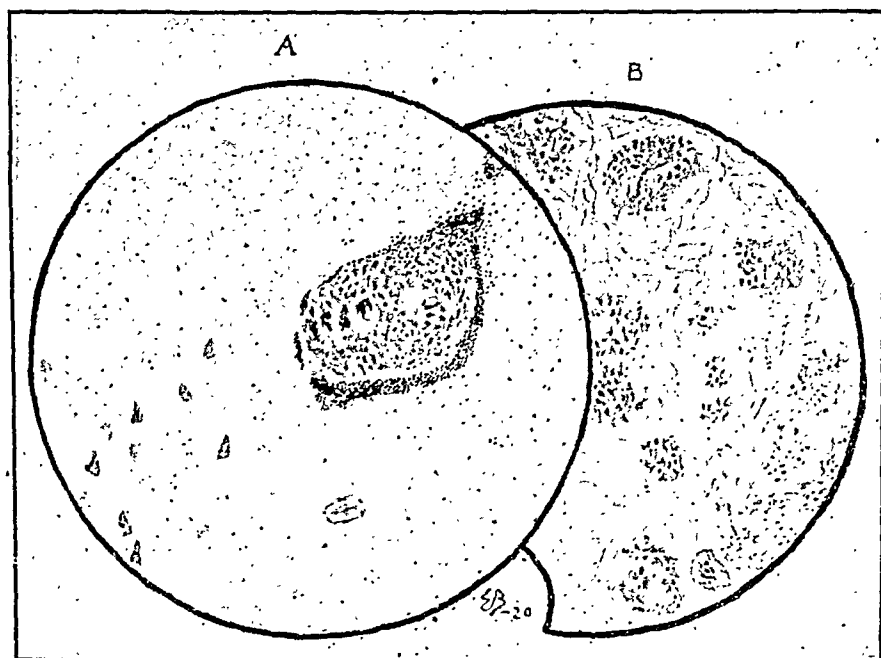


FIG. 6.—A, section through anterior horn, showing a large epithelioid tubercle; ganglion cells to the left. B, tubercles on the surface of the fourth ventricle, composed of epithelioid cells and free from reactive changes.

of the marked proliferation of glia cells in the wall of the lateral ventricle as an indication of the chronic nature of the process. The case is noteworthy especially on account of the marked tendency of tubercles to develop along the bloodvessels into the substance of the brain and cord, thus giving rise to a condition that may be designated as a tuberculous encephalitis and myelitis as well as poliomyelitis. The poliomyelitic changes were also secondary to the process in the membrane and due to perivascular spread, reminding one of the changes in epidemic poliomyelitis and lethargic encephalitis. In our work on epidemic poliomyelitis Scheel and I¹¹ advanced the idea that the virus of poliomyelitis infects the leptomeninges first and then the arachnoid fluid, the infection spreading along the vessels, particularly the arteries, and thus reaches the anterior horns in the cord. We pointed out that in tuberculous and other forms of meningitis a similar extension into the substance of the central nervous system may take place, and the case now described lends strong support to the view that infection may reach the substance of the brain and cord in the way indicated. It would seem that in lethargic encephalitis also extension may take place in this way.

Cases like the one described would seem to be rather infrequent, particularly such marked degree, but less marked examples of tubercle conglomeration over limited areas of the brain surface, without diffuse meningitis, and even with focal symptoms, are probably not so rare. I observed a case of this kind in a man, aged thirty years, who had been sick for about four months with paresis in the left arm; there were signs of tuberculous meningitis here and there, most over the right convexity, and then large conglomerate tuberculous masses in and about the right sulcus centralis, the process being of a chronic nature with tendency to heal.

From the results of the observations at hand it may be concluded that tuberculous meningitis may heal, and even in cases in which rather extensive lesions with exudate and tubercle formation have developed. What may be the reason that tuberculous meningitis occasionally takes this course? It may depend on the nature of the infection, and it seems that this curable form of meningitis has occurred largely in persons who have suffered from chronic and relatively benign forms of tuberculosis. It is probable, however, that a more important factor is increased resistance on part of the body, which bears some relation to the age of the patient. It is interesting to note that while about 60 per cent. of all cases of tuberculous meningitis occurs in the first two years in life and quite regularly result in death, the cases with recovery have occurred in older children and in adults. Bokai found that in 18 such cases the age ran from two to twelve years and in 12 cases from sixteen

¹¹ Pathologisch-Anatomische Untersuchungen über Poliomyelitis und verwandte Krankheiten, Videnskapselsk's Skr. 1 Math. Naturv. Klasse, 1907, nr. 5.

to forty-four, and in the recently observed cases it concerned adults. Consequently it would seem that an increased resistance must be of considerable importance.

With reference to the prognosis, it may be noted that while epidemic meningitis frequently terminates in a chronic condition with internal hydrocephalus and other serious changes, tuberculous meningitis, even when extensive lesions have formed, may heal without any serious defects. In the case now reported there was an internal hydrocephalus in the early stages.

CLASSIFICATION OF GOITER: AN ANALYSIS OF ONE HUNDRED CASES.¹

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THE classification and nomenclature of goiter have always been unsatisfactory, for the reason that in spite of the large number of cases operated on and the extensive material for pathologic examination no standardization of title has resulted.

It is generally agreed there are two great classes of goiters: The simple goiter, without symptoms other than pressure, and the toxic goiter, with symptoms referable to various organs other than the thyroid gland.

Plummer² and Wilson,³ since 1914, have written regarding the clinical and pathologic difference in cases of toxic goiter, but there is little evidence in the literature that their views have been accepted. Plummer, in a paper from the Mayo Clinic, read in June, 1919, divided the toxic type of goiter into two groups, one of which he called hyperthyroidism and the other exophthalmic goiter. Our experience with goiter is in accordance with this division. Our series of cases is not sufficiently large to prove the points to be made nor is there sufficient accuracy or detailed clinical data to be certain of the proper classification of borderline cases; but we wish to record our experience in line with the above writings.

Simpson,⁴ in a recent article, has classified goiter from pathologic specimens sent to him for diagnosis, and his conclusions are largely in accord with our own observations.

We wish to present the last 100 cases of goiter operated on in St. Luke's Hospital during the period of eighteen months. All

¹ Read before the Richmond Academy of Medicine and Surgery, June 22, 1920.

² Keen's Surgery, vol. vi; AM. JOUR. MED. SC., December, 1913; Collected Papers of the Mayo Clinic, 1914 to 1918.

³ Journal-Lancet, xxiv, 4.

⁴ Surg., Gyn. and Obst., February, 1919.

cases admitted to the surgical service were operated on except 3. One of these was a woman, aged fifty-five years, with extensive myocardial and renal degeneration, who was treated by the roentgen-ray and has since died. The second was a man, aged forty-five years, with thyroiditis following influenza and associated with chronic and severe myocarditis and aortitis. The third was a woman, aged forty-seven years, with a large, very hard goiter and bony metastasis in the lumbar spine. The diagnosis of carcinoma of the thyroid with spinal metastasis was made and she was considered hopeless. These 3 cases are not included in this series. It should be noted here that cancer of the thyroid will occur in about 1 per cent of all goiters and should be considered when dealing with this condition.

We have divided our cases into three groups:

Group I contains the simple goiter, about which there is little to be said. They have few symptoms occasionally complaining of pressure, as evidenced by hoarseness, obstruction to breathing and difficult swallowing. They come to operation for relief of these symptoms, or as is more frequent, for a correction of the deformity.

A summary of the cases in this group is as follows:

Number, 61.

Sex: Males, 4; females, 57.

Age: Twelve to sixty years. Average, thirty-two and a half years.

Duration: Two months to twenty-five years. Average, seven and a half years.

Growth: Gradual increase in size in all cases except 3; these of twenty-five, ten and five years' duration had grown more rapidly in the year preceding operation. The pathologic report in all 3 cases was cystic colloid goiter.

Tachycardia: One case.

Tremor: The fine fibrillary tremor was absent in all cases. A few had a gross tremor. Loss of weight was noted in only 2 cases.

Nervousness: Thirty-six per cent. of the cases were nervous but none were of the toxic type of nervousness.

Recurrence: Two cases were recurrent. The pathologic reports were cystic and cystic colloid goiter.

PATHOLOGIC REPORT.

Simple adenoma	12
Colloid goiter	24
Cystic goiter	10
Fetal adenoma	10
Hematoma	1
Colloid with parenchymatous hyperplasia	1
Adenoma with parenchymatous hyperplasia	1
No report	2
Total	61

In this group it should be noted that 2 cases were recurrent, both of cystic type. One case was a hematoma of seven years' standing, resulting from a severe strain in a wrestling match; the patient was a powerfully built young man. Two cases showed parenchymatous hyperplasia in addition to colloid and adenomatous goiter, and though clinically in this group, must be considered as borderline cases with Group II. Both of these cases had goiter of short duration, and without surgical intervention would have developed hyperthyroidism and have been definitely in Group II.

To avoid confusion the pathology of goiter, with special reference to our classification, should be mentioned. The simple adenoma is comparable to the adenoma found in other glands. The colloid goiter is composed of multiple dilated tubules filled with colloid material. The fetal adenoma is composed of alveoli lined with a single layer of cells embedded in hyaline material.

The toxic goiter cases we formerly considered as varying degrees of the same pathologic process, but in the light of Plummer's papers and our own observations we would divide them into two groups, with rather decided clinical contrast.

Group II we call hyperthyroidism, as will be described later.

Group III we call exophthalmic goiter.

Group II presents a very interesting picture. The patients are middle age and have had a goiter for a long time without symptoms. These quiescent goiters suddenly begin to grow, and coincident with the growth the patients become restless and nervous; they have attacks of palpitation, the heart-rate becomes accelerated and they lose weight, but they do not have the fine tremor of the third group nor do they have the exophthalmos. One case in this group had the toxic symptoms for two years, but there was no exophthalmos; all cases in Group III of that duration had the typical exophthalmos. Experimentally this group can be reproduced by feeding thyroid extract, and they promptly recover when the feeding is stopped.

A summary of the cases in this group is as follows:

Number: 20.

Sex: Male, 1; females, 19.

Age: Thirty-four to fifty-eight years. Average, forty-seven years.

Duration: Two months to thirty years. Average, eleven years.

Growth: Recent growth of goiter in 10 of 14 cases recorded, 77 per cent.

Tachycardia: Present in 35 per cent.

Exophthalmos: Absent in all cases.

Tremor: The fine fibrillary tremor was absent in all cases. Gross tremor in 35 per cent.

Loss of Weight: 5 to 100 pounds in 40 per cent.

Nervousness: All these patients complained of being nervous. In one case, the only postoperative death, it amounted to a dementia.

PATHOLOGIC REPORT.

Colloid with parenchymatous hyperplasia	7
Fetal adenoma	3
Colloid	6
Simple adenoma	1
Cystic	1
Fetal adenoma with parenchymatous hyperplasia	1
No report	1
Total	<hr/> 20

The patients in Group II have for years had the pathology described for Group I. They still have this pathology, but some of the tubules have papillary projections into the lumina from cellular proliferation, and, besides, there are a few areas of closely packed tubules containing little or no colloid material.

Group III embraces the patients with the classic symptoms of exophthalmic goiter; they present a line of symptoms including all in Group II, but in addition definite points which put them in a separate class. We will not attempt to go into theories of the cause or even the pathology of exophthalmic goiter outside of the thyroid gland. These patients have small goiters; they have had symptoms for a relatively short while and the onset of the toxic symptoms is coincident with or previous to the appearance of the goiter. Two of these cases were clinically put into this group, but the pathologic report corresponds to the picture to be expected in Group II. It is interesting to note that one of these two was a borderline case and had no exophthalmos, while the other is a frank exophthalmic which we consider as developing independently rather than on the existing adenoma. Exophthalmos has been considered as a symptom frequently absent in Graves's disease; of these cases 60 per cent. have exophthalmos, while in the 6 cases without it 5 were of one year or less duration and the sixth was a doubtful Group III. Practically all of the cases have tremor, tachycardia and the typical nervousness. The tremor in these cases is the fine fibrillary motion of the fingers quite distinct from the gross tremor seen in Group II. The tachycardia is much more pronounced in this than in the preceding group.

A summary of the cases in this group is as follows:

Number, 19.

Sex: All females.

Age: Fifteen to fifty-one years. Average, thirty-three.

Duration: Two months to seven years. Average, two years.

Growth: Recent growth of goiter in 8 of 14 cases recorded, 57 per cent.

Tachycardia: Present in 86 per cent.

Exophthalmos: Present in 60 per cent.

Tremor: The fine fibrillary tremor present in 86 per cent.

Loss of Weight: Ten to forty pounds in 30 per cent.

Nervous: All were typically nervous, as evidenced by rapid speech, movement of limbs, excitability, etc.

PATHOLOGIC REPORT.

Severe papillary hyperplastic parenchymatous	14
Simple adenoma with parenchymatous hyperplasia	1
Colloid with parenchymatous hyperplasia	1
No report	3
Total	<hr/> 19

The pathology typical of Group III is the hyperplastic parenchymatous goiter, which is composed of closely packed tubules lined with multiple rows of large cells with little or no colloid material.

We will dismiss the case in Group I, the simple goiter with the brief discussion already given. We believe, however, that the demonstration of hyperthyroidism developing in the simple goiter will give additional importance to the removal of this quiescent but potentially dangerous pathology.

It has been our custom until recently to classify all the other cases with toxic symptoms as varying degrees of the same process, and although we have used a variety of terms we have meant the same disease, and, as a rule, have simply called it hyperthyroidism. We now believe, however, that there are two very definite groups of these cases and propose to call one, Group II, hyperthyroidism to signify that the cause of the toxemia is an increased secretion and absorption of the thyroid secretion. In Group III we adhere to the time-honored title exophthalmic goiter, because we have no better name. We feel that this condition is a clinical entity, and although we want to avoid the mooted questions of pathology and etiology, we believe neither is limited to the thyroid gland.

The clinical grounds for this grouping we believe to be sufficient. The patients in Group II are older women, forty-seven years of age against thirty-three in Group III. They have had the goiter for a number of years, eleven as opposed to two. The goiter has given no symptoms for long periods; the toxemia has been present from six months to two years, and is coincident with the recent growth of the gland, while the exophthalmic, or Group III, has had the symptoms as long as the goiter, and in some cases even without apparent enlargement of the gland. Perhaps the most striking difference in symptomatology is the exophthalmos; it is absent in all cases in Group II but present in 60 per cent. of Group III, being absent only in early cases or in cases doubtfully classified. We believe that cases in Group II will never develop exophthalmos while all cases in Group III will have it if of long enough duration. A larger percentage of cases in Group III have tachycardia, 86 per cent. against 35 per cent. in Group II, but no other practical difference was noted in this symptom. The tremor in the two groups bears the same percentage ratio as tachycardia, but the tremor of the exophthalmic is more definitely beyond the patient's control and more rapid with shorter excursions than that of the hyperthyroid.

Pathologically the grouping is quite interesting. The tissue was examined by Dr. Hopkins, and in his absence by Dr. Budd, quite independently of any clinical data, and although the reports are by no means positive proof of our position, we feel that for routine examination they are confirmatory, and with more detailed study we believe they will tally more exactly. In Group II all cases originally had a goiter of simple type; 40 per cent. of these goiters showed an active hyperplasia in addition to the old goiter, 15 per cent. were fetal adenomata and 40 per cent. showed only the simple type of goiter.

In some of these last cases the same slide would show an old pressure atrophy and a recent hyperplasia of the cellular elements, which has been described fully by Wilson.

In Group III only two specimens, 10 per cent., showed goiter of simple type with hyperplasia of the cellular elements, and of these one was doubtfully classified. Fourteen, 74 per cent., showed the typical papillary hyperplasia of the parenchyma.

Conclusions. Toxic goiters should be regarded as belonging in two definite groups, first, those in whom the intoxication is due to a recent proliferation of parenchyma in an old goiter, our Group II, and second those in which the thyroid hyperplasia is primary and probably associated with other pathology, our Group III.

The simple goiter, Group I, should be surgically removed not only for relief of pressure and for cosmetic improvement, but also to remove the danger of hyperthyroidism and cancer which may develop as the patient and the goiter become older.

The patients in Group II can be relieved by removing the goiter; they may expect perfect recovery unless the operation is delayed until thyroid stimulation has seriously damaged other vital organs. They will become progressively worse if not treated, but will not develop into Group III, the exophthalmic goiter.

Group III cases are improved by surgical treatment; the prognosis, however, is not comparable to what may be expected in Group II. We believe that the best results claimed in treating exophthalmic goiter have been due to operations on cases in Group II which is not exophthalmic goiter. The converse, however, is true—that is, that the poor results are in cases which we would classify in Group III. In spite of this, however, we believe that surgery is the best treatment now known for exophthalmic goiter.

The roentgen-ray and radium treatment of goiter should be confined to cases in Group III, and it is possible that with further development the radiologist may be able to take precedence over the surgeon in Group III cases.

I wish to acknowledge my indebtedness to Dr. Stuart McGuire, on whose service these cases were operated, and to Dr. E. G. Hopkins, who examined the pathologic specimens.

MULTIPLE FLUID COLLECTIONS IN THE CHEST IN THE COURSE OF THERAPEUTIC PNEUMOTHORAX.¹

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AND

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It is the purpose of this paper to call attention to multiple fluid collections in the chest that occur in the course of induced pneumothorax. This condition cannot be detected by physical examination, and it is recognized only by the characteristic multiple fluid-levels shown on roentgenologic examination. There is usually seen one or more secondary fluid-levels superimposed upon and parallel to the level of the main effusion, and under the fluoroscope a fluid wave can be elicited on each level independently. Among 32 cases of hydropneumothorax we encountered this condition in 5 instances.

It is obvious that the essential factor entering into the causation of such multiple fluid collection is extensive pleuritic adhesions, but the exact mechanism of their production requires further explanation. It would be reasonable to assume that this condition is due to adhesions so distributed as to divide the potential pleural cavity into two or more non-communicating compartments, so that when attempts to induce pneumothorax are made at different points of the chest, two or more pneumothorax pockets may be produced, and when an effusion subsequently supervenes the fluid accumulates in each compartment separately, or pneumothorax is induced in one compartment and a spontaneous pneumothorax occurs in a compartment adjacent thereto.

But while the just described mechanism explains the causation of multiple localized hydropneumothoraces in one of our cases it does not do so in the others that came under our observation, inasmuch as we succeeded in inducing a fair pneumothorax in these cases at the first attempt, and all subsequent punctures were made in areas where the fluoroscope showed a definite pneumothorax, thereby excluding the possibility of the existence of independent pockets.

In view of frequent roentgenologic examinations, before and after the development of the effusions, we are led to believe that in most cases this condition is due to sheet-like adhesions spreading in hammock-like fashion from the visceral pleura across the pneumothorax area to the chest wall. These adhesions, when an effusion supervenes, serve as a receptacle to catch the fluid secreted from the pleural surface above their insertion, and at the same time part

¹ From the Montefiore Home Country Sanatorium, Bedford Hills, N. Y.

of the main effusion below may also be entrapped therein by change of the patient's posture.

It is pertinent to interpolate that certain multiple fluid collections are due to fluid-containing cavities coexisting with hydropneumothorax.

REPORT OF CASES.

MULTIPLE FLUID COLLECTIONS DUE TO A SPONTANEOUS PNEUMOTHORAX SUPERIMPOSED UPON A LIMITED INDUCED PNEUMOTHORAX.

CASE I.—A. C., aged twenty years, admitted August 12, 1918, with a typical history of active pulmonary tuberculosis and recurrent attacks of pleurisy on the right side. Examination showed extensive, active tuberculosis on the right side. Right pneumo-

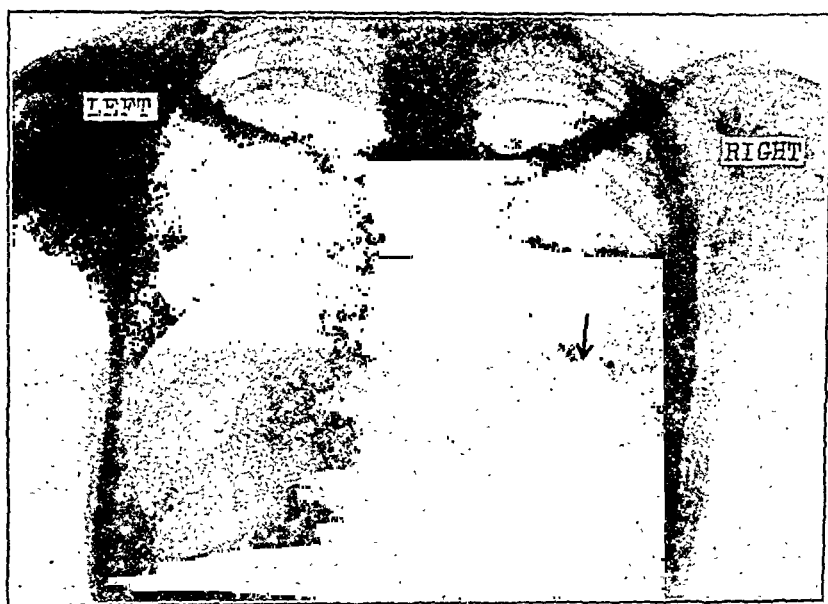


FIG. 1.—Case A. C. Note two fluid levels on right side.

thorax was induced on December 2, 1918. Fluoroscopic examination after the first few inflations showed a fair collapse of the right upper lobe; the lower lobe was held down by adhesions. On January 19, 1919, the patient developed chills and fever and hydropneumothorax was detected two days later.

Physical examination subsequently showed the fluid to be up to the third rib, breath sounds and whispered voice being practically inaudible below that level.

On January 22 the patient was seized with a severe stabbing pain in the right lower midaxillary region, and when she was first seen

she was dyspneic and quite cyanosed. Physical exploration of the chest revealed amphoric whisper and distant amphoric breathing below the described level. The possibility of a spontaneous pneumothorax was suggested, inasmuch as previous fluoroscopic examinations showed that the lower lobe was not at all collapsed. On January 28 fluoroscopic examination disclosed two definite fluid levels, each giving an independent splash. The two pockets seemed to be non-communicating. A roentgenogram (Fig. 1) taken the same day confirmed the fluoroscopic findings.

It is evident that in this case the two fluid levels were caused by two independent pockets of hydropneumothorax, one artificial and one spontaneous.



FIG. 2.—Case M. L. Note adhesions on level of second and third ribs.

MULTIPLE FLUID COLLECTIONS CAUSED BY HAMMOCK-LIKE ADHESIONS.

CASE II.—M. L., aged twenty-five years, housewife, admitted March 10, 1919, with extensive and active left-sided tuberculosis. Left pneumothorax was induced July 30, 1919. A roentgenogram taken October 21, 1919 (Fig. 2), shows a fairly complete collapse of the left lung except that there are bands of adhesions stretched across the pneumothorax area to the chest wall on the level of the second and third ribs. During November, 1919, the patient developed an effusion, and a roentgenogram (Fig. 3) taken December 19,

1919, shows a hydropneumothorax with two definite fluid levels, one on the level of the second rib and one on the level of the fifth rib.

It is evident that in this case the upper compartment of fluid collected on top of adhesions that have been present prior to the induction of pneumothorax, inasmuch as the upper fluid level corresponds exactly to the level of the adhesions that were definitely seen before the effusion developed.

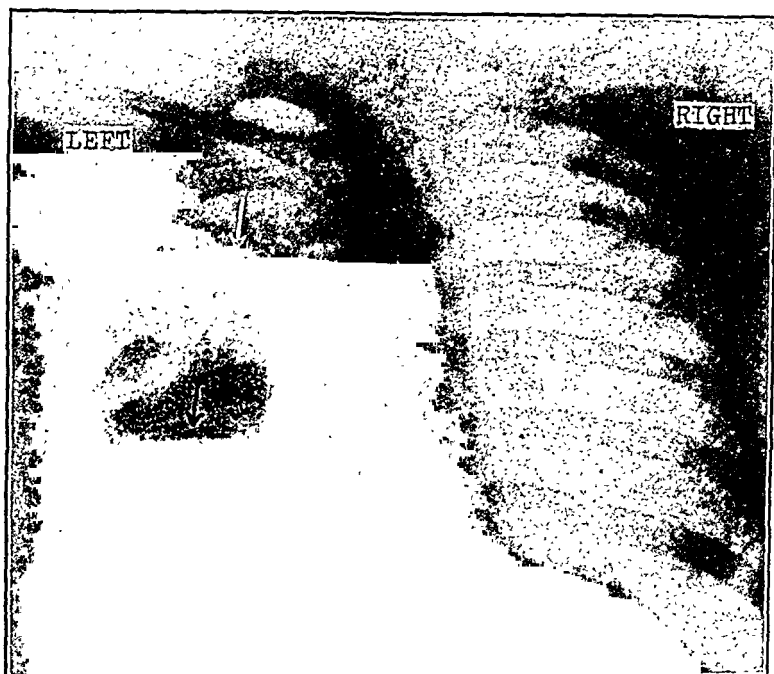


FIG. 3.—Case M. L. Note fluid levels on left. The upper level corresponding to location of adhesions as seen in Fig. 2.

HAMMOCK-LIKE ADHESIONS AS A RESULT OF PREEXISTING THICKENED INTERLOBAR SEPTUM PRODUCING MULTIPLE FLUID LEVELS.

Sheet-like adhesions are sometimes the result of pathologic changes in the interlobar septum. When pneumothorax is induced in these cases the parietal and visceral pleurae remain adherent at a point corresponding to the interlobar septum, and the lung may be collapsed above and below that level, thus leaving a shelf-like sheet of fibrous structure on which fluid may accumulate. The following case illustrates this condition:

CASE III.—M. P., aged twenty-two years, admitted July 19, 1919, with a typical history of pulmonary tuberculosis. Examination showed tuberculous involvement of the right upper and middle lobes and left apex. A roentgenogram (Fig. 4) showed diffuse infiltration throughout the upper two-thirds of the right lung, with

multiple small cavities in the infraclavicular region. At the level of the third rib anteriorly there was a small, very dense, triangular

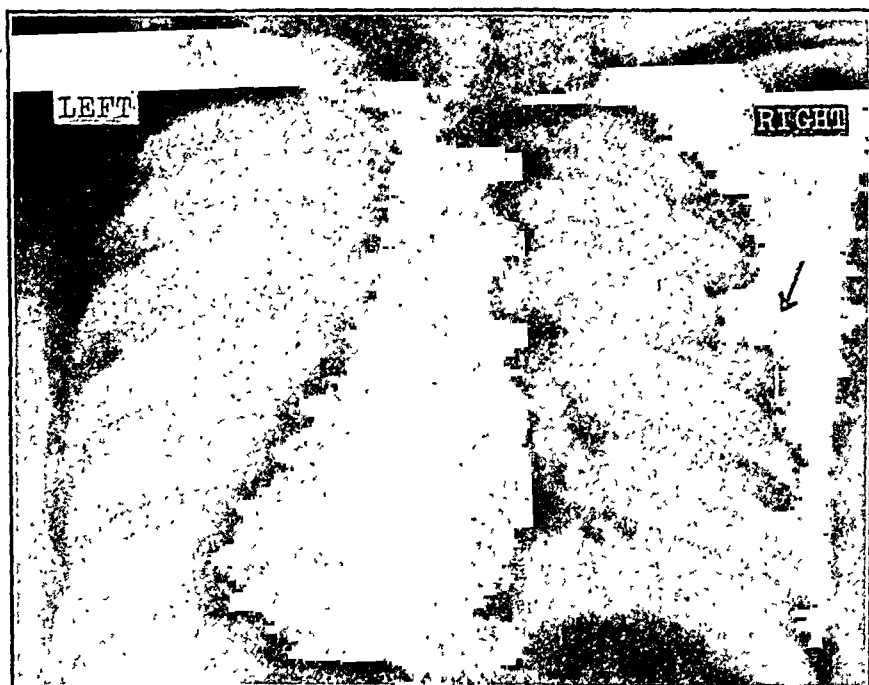


FIG. 4.—Case M. P. Note density in region of interlobar septum on right.

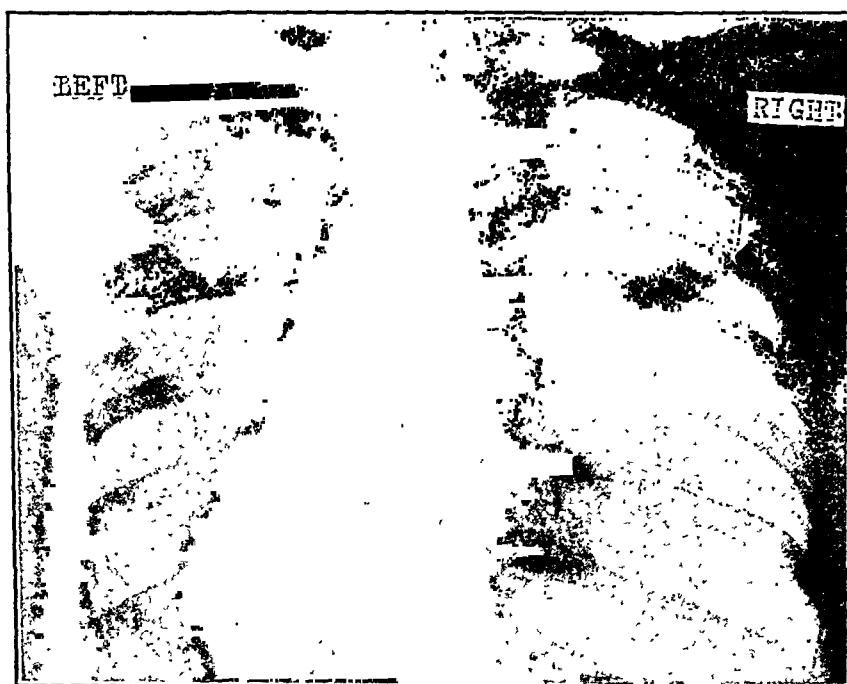


FIG. 5.—Case M. P. Note adhesions in location corresponding to location of thickened interlobar septum seen in Fig. 4.

area, the base of the triangle being toward the periphery. This was undoubtedly a thickened interlobar septum.

A right pneumothorax was induced on August 8, 1919, and a roentgenogram (Fig. 5) taken six weeks later showed an irregular area of pneumothorax occupying the major part of the right pleural cavity, and there was a heavy band of adhesions running horizontally from the lung to the chest wall on the level of the third rib. This point corresponded exactly to the location of the thickened interlobar septum seen on a previous plate. During November, 1919, the patient developed an effusion, and a roentgenogram (Fig. 6) taken November 25, 1919, showed three fluid levels, the



FIG. 6.—Case M. P. Plate taken in oblique position. Note three fluid levels. The uppermost probably due to a fluid-containing cavity. Middle level in location of thickened interlobar septum seen in Figs. 4 and 5.

main fluid level at about the fourth rib, a secondary fluid level at the third rib and a small fluid collection at the third space near the root, each fluid level giving an independent fluid wave on fluoroscopy.

In this case it is obvious that the hammock-like adhesion on which the secondary fluid collection accumulated is due to pre-existing pathologic changes in the interlobar septum, as a comparison of Figs. 4, 5 and 6 will readily show. The small fluid collection at the third space near the root is most probably due to a cavity partly filled with fluid.

MULTIPLE FLUID LEVELS CAUSED BY SHELF-LIKE ADHESIONS FORMED BY THE ORGANIZATION OF THE EXUDATE PRESENT.

In the above-described cases the adhesions that caused the secondary pockets of fluid were present prior to the induction of the pneumothorax, but we also observed cases in which there were no preëxisting adhesions in the pneumothorax area; but as a result of the organization of part of the exudate, shelf-like septa were formed. These newly formed fibrous structures supported part of the fluid, and on roentgenologic examination multiple fluid levels were seen. The following cases illustrate this condition:



FIG. 7.—Case G. F. Note small adhesions at level of second space and absence of adhesions below.

CASE IV.—G. F., female, aged twenty-six years, housewife, was admitted May 5, 1919, with extensive, active tuberculosis involving the entire right lung and the left apex. Right pneumothorax was induced June 19, 1919, and a roentgenogram (Fig. 7) taken June 24, 1919, shows a fairly complete collapse of the entire right lung. The collapse was specially marked at the base, the lung being collapsed upward and inward. There was, however, a band of adhesions at the level of the second space running from the lung to the chest wall.

During the month of September, 1919, the patient developed an effusion, and a roentgenogram (Fig. 8) taken September 24, 1919, showed three levels of fluid at the levels of the second, fifth and

sixth ribs respectively. Fluoroscopy showed independent fluid waves on each fluid level.

In this case, besides the fluid collection in the region of the pre-existing adhesions at the second space, there is another secondary fluid level at the fifth rib, where, as seen from the previous plate, there were no adhesions. It is certain, therefore, that the adhesions causing this secondary fluid-level were newly formed as a result of the organization of the exudate.

CASE V.—R. P., male, aged forty-eight years, tailor, was admitted January 14, 1918, with extensive tuberculosis involving the entire left lung. Left pneumothorax was induced May 13, 1918.



FIG. 8.—Case G. F. Note three fluid levels. The uppermost in region of previous adhesions. The middle in an area previously free from adhesions.

Fluoroscopy, after the first few inflations, showed a localized pneumothorax occupying the axillary portion of the lower half of the pleural cavity.

During December, 1918, the patient developed an effusion and a roentgenogram taken January 7, 1919 (Fig. 9), showed three fluid-levels within the area previously occupied by free pneumothorax, the relation of the three fluid-levels to each other being somewhat step-like in character. Under the fluoroscope three independent fluid waves were seen.

Here, again, the triple fluid-levels developed in an area previously

free from adhesions, so that the organization of the exudate was undoubtedly the cause of the secondary collections of fluid.

Summary. 1. Careful observation of 32 cases of hydropneumothorax disclosed the presence of multiple fluid collections in 5 cases.

2. This condition could not be detected without the aid of the roentgen ray, which showed characteristic multiple fluid-levels.

3. Two or more independent hydropneumothorax pockets may be produced as a result of attempts to induce pneumothorax at different levels of the chest or a localized spontaneous pneumothorax may occur adjacent to a pocket of artificial hydropneumothorax.

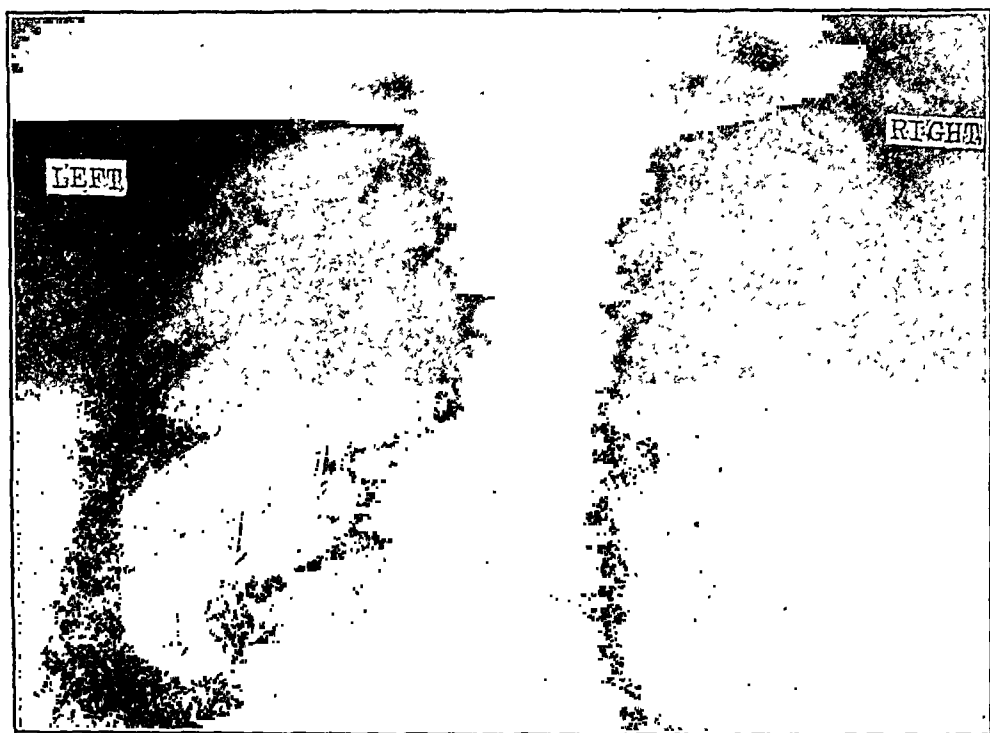


FIG. 9.—Case R. P. Note three fluid levels on left side.

4. The most important factor in the causation of this condition is pleuritic adhesions which spread out in hammock-like fashion from the visceral pleura across the pneumothorax area to the chest wall. These adhesions may be present before the induction of the pneumothorax and may occasionally be the result of a thickened interlobar septum, or they may be newly formed as a result of organization of the exudate.

5. The coexistence of a fluid-containing cavity with a hydropneumothorax may also give rise to multiple fluid levels.

NEPHROLITHOTOMY IN HORSESHOE KIDNEY.

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THE occurrence of pathology associated with a horseshoe kidney is sufficiently rare to warrant report.

The horseshoe kidney is one variety of the congenital anomalies met with in the kidney. During the entrance of the fetal kidneys into the abdominal cavity and their ascent to the normal position it is thought that occasionally they are caught in the ring formed by the umbilical arteries (Lewis and Papez). During this arrest in movement, fusion of the two kidneys is thought to take place.

Fusion may occur in any manner. One kidney may be superimposed upon the other ("disk kidney") or the upper pole of one kidney may become fused with the lower pole of the other ("sigmoid kidney"). More frequently, however, fusion is between the two upper or the two lower poles, the lower poles being most commonly united.

The isthmus connecting the two poles is of mesoblastic or parenchymatous tissue and varies in thickness from a few centimeters to the normal thickness of the kidneys.¹ The concavity is usually down and the greater the thickness of the isthmus the more caudal is the kidney.

The pelves and ureters are usually ventral to the kidney. The pelves are frequently anomalous in containing two rows of calices (dorsal and ventral) and no major calix. The blood supply is almost always anomalous. Renal arteries may be found in numbers of six or more, passing to each kidney proper, with corresponding veins.

Occurrence. Roth² found five horseshoe kidneys in 1630 autopsies. The Berlin Pathological Institute reported six in 6200 autopsies. Statistics of Guy's and the London Hospital together with those of Victoria Hospital show 16 horseshoe kidneys in 13,505 autopsies.³ The average incidence from these and other figures is 0.7 per cent. The incidence in males has been found to be much higher than that in females, some reports estimating it at 14 to 1.

Pathology. Horseshoe kidney is encountered relatively more frequently in the operating room than at autopsy. This fact is taken to indicate that the horseshoe kidney, by reason of its low position and the twist in the renal pelves to attain their ventral position, is predisposed to pathology. The most common lesions

¹ Lipschutz and Hoffman: *Ann. Surg.*, 1918, lxxviii, 39.

² *Veroeffentlichungen d. Hufelandischen Gesellschaft*, 1910.

³ Oehler: *Beitr. z. klin. Chir.*, 1914, lxxxix, 223.

are hydro- and pyonephrosis.⁴ Bräasch⁵ reporting the horseshoe kidneys which came to operation at the Mayo Clinic, found hydro-nephrosis in 4, sarcoma in 1 and essential hematuria in 1, while 4 were without gross pathology and were met with accidentally.

Diagnosis. The diagnosis is occasionally made by inference. If both kidneys are palpated in a distinctly caudal position, and particularly if their lower poles are felt to incline toward the midline, the diagnosis should be entertained. The entire horseshoe mass may be palpated occasionally. Israel⁶ and Newman⁷ have been able to do so in single cases. The pyelogram may show the pelves lower than normal and distended. Frequently the contrast fluid will run out of the pelves as soon as it is put in because of their vertical position.⁸ If a stone is present the shadow may be lower than normal, as opposite the second or third transverse lumbar processes.⁹

Literature. Most of the operations upon horseshoe kidney have been directed against a pyo- or hydronephrosis. Exposure and mobilization and control of hemorrhage are the main difficulties.

Zondek,¹⁰ Rovsing,¹¹ Oehler,¹² Socin,¹³ and the Mayos¹⁴ have successfully removed part of the distended pelvis. Operations for stone have been less frequent. Rovsing¹⁵ reviews 4 cases of horseshoe kidney. In one of these an attempt was made to remove a stone without success. After operating through the lumbar incision in his first 2 cases Rovsing strongly advised the transperitoneal route. In 2 cases Rovsing divided the isthmus and in 1 case obtained complete relief from pain, referred from one side of the back to the other, which he considers characteristic of horseshoe kidney *per se*.

Rumpell¹⁶ successfully removed a stone which cast a shadow opposite the second and third lumbar vertebræ. There was an associated pyonephrosis. The lumbar incision was used. In this case collargol instilled into the kidney pelves ran out as soon as it was put in.

Lange¹⁷ successfully removed a stone through the lumbar incision. No pyelogram was made.

⁴ Tr. Am. Assn. Gen.-Urin. Surg., 1913, viii, 289.

⁵ Lipschutz and Hoffman: Ann. Surg., 1918, lxxviii, 39.

⁶ Chirurg. klin. der Nierenkrankheiten, Berlin, 1901.

⁷ Lancet, 1917, ii, 236.

⁸ Vorhoeve, N.: Jour. de radiol. et electrol., 1919, iii, 414.

⁹ Rumpell: Centralbl. f. Chir., 1902, xxix, 1091.

¹⁰ Arch. f. klin. Chir., 1914, cv, 676.

¹¹ Ztschr. f. Urol., 1911, v, 586.

¹² Oehler: Beitr. z. klin. Chir., 1914, lxxxix, 223.

¹³ Beitr. z. klin. Chir., 1889, iv, 197.

¹⁴ Tr. Am. Assn. Gen.-Urin. Surg., 1913, viii, 289.

¹⁵ Loc. cit.

¹⁶ Centralbl. f. Chir., 1902, xxix, 1091.

¹⁷ Ann. Surg., 1901, xxiv, 581.

Newman¹⁸ diagnosed horseshoe kidney by palpation and attempted removal of a stone by the transperitoneal route.

Krotoszyner¹⁹ operated on a patient with bilateral nephrolithiasis in which the pyelogram showed no abnormality. Horseshoe kidney with pyonephrosis was encountered. One stone was removed, with death in five days from uremia and sepsis. The lumbar incision was employed.

The most recent case recorded is the interesting one of Primrose,²⁰ where the patient presented a palpable tumor of the abdomen. Operation revealed a horseshoe kidney, of which one organ was consumed by a malignant cyst in which many calculi were found. The calculi were removed and the patient survived nine months. In dealing with this condition, Primrose sutured together the margins of the incisions in the anterior and posterior parietal peritoneum, thus marsupializing the mass.

PROTOCOL OF CASE. J. A., white, male, a hatmaker, aged twenty-nine years, was admitted to the University Hospital, Philadelphia, April 6, 1920.

Two years previously patient began to have a pain in his left lumbar region. The pain was sharp but not of great severity, and would last from a few hours to several days. There was no radiation of pain and no urinary symptoms.

In August, 1919, patient had a very severe attack of pain in the left lumbar region, with radiation to the left testicle. Patient was forced to go to bed. The pain lasted several days, and for two days thereafter the urine was reddish. Since then the patient has had four similar attacks. With them there is urgency but no pain or frequency. Between the attacks patient has a constant, dull pain in the left lumbar region but which does not radiate.

There are no symptoms referred to the other systems and the past medical history is negative.

Examination reveals a well-muscled Italian, in evident good health. Positive findings are as follows:

Severe pyorrhea; slight cervical adenopathy; epitrochlear glands are palpable; a few scattered rales at the left base.

The lower pole of the left kidney is vaguely palpable and slightly tender. The upper left quadrant of the abdomen is slightly resistant to palpation. About one inch to the left of the umbilicus, and on a level with it, there is well-defined tenderness. Pressure over the corresponding spot on the right side causes sharp pain in the left hypochondrium.

Blood-pressure 130-75.

The urine shows 10 to 12 red blood cells and 8 to 10 white blood

¹⁸ Lancet, 1917, ii, 236.

¹⁹ Ann. Surg., 1917, lxx, 565.

²⁰ Jour. Am. Med. Assn., July 3, 1920, lxxv, 12.

cells per high-power field, with a trace of albumin, and occasional hyalin casts. The blood count is normal. Phthalein elimination (intramuscular) is 37 per cent. in the first hour and 20 per cent. in the second hour.

Cystoscopy (Dr. Alexander Randall) discloses an entirely normal bladder and ureteral orifices. No difficulty was encountered in injecting the contrast fluid into the kidney pelvis, and it stayed in position readily.

The roentgen ray shows a stone about 1.5 cm. in diameter in the left kidney. Pyelogram shows both pelves slightly distended and several calices of the left pelvis pointing forward toward the spine, suggesting rotation (Dr. Henry Pancoast).

A diagnosis of stone in the left kidney was made.

Operation, April 9, 1920. Left lumbar incision. The upper pole of the left kidney was exposed and freed without difficulty. The lower pole, however, could not be dislocated even after prolonging the incision downward. On palpation it appeared lower than normal, and it could be felt extending across the lumbar vertebræ. Since it was evident that a horseshoe kidney had to be dealt with, it was deemed advisable to approach the kidney by another route and the incision was closed around a cigarette drain.

Convalescence was uneventful. Two weeks after operation the patient had a severe attack of renal colic which lasted for about twenty-four hours, and three weeks later a second attack of like severity was experienced. Roentgen ray showed the stone in its original position.

Operation, June 4, 1920. Dr. John B. Deaver. A left rectus incision was made. The great omentum and the intestine were moved out of the field to the right. The sigmoid was found to have an unusually short mesentery. An incision was made in the outer leaf of the descending mesocolon and the descending colon was mobilized and pushed to the right. The left ureter was identified where it crossed the left iliac artery. The ureter was traced upward until the pelvis and lower pole of the left kidney were reached. The lower pole of the left kidney was found to be continuous with that of the right by an isthmus about 8 cm. in width.

The pelvis of the left kidney overhung the left kidney in a ventral position. It was distended to about twice its normal size. Encircling the upper part of the left ureter several large anomalous veins ramified over the pelvis. The artery was posterior to the ureter and the veins.

The upper pole of the left kidney was disclosed and mobilized. No stone could be felt in the pelvis. An incision was made between two large veins and the finger detected a stone in one of the uppermost calyces. The stone was removed. It was about 1.5 cm. in diameter and of the mulberry type. The pelvis was closed with

inverting Lembert sutures. Two rubber drainage tubes were put through the lumbar scar. The posterior parietal peritoneum was sutured and the abdomen closed without drainage.

Convalescence was rapid and uneventful. There has been no recurrence of symptoms to date.

The case is of particular interest in that from the abdominal signs the possibility of horseshoe kidney should have been entertained. It also emphasizes the fact that a difficult or impossible procedure through the lumbar route may be converted into a comparatively simple one by employing the transperitoneal route.



Conclusions. 1. The possibility of horseshoe kidney must be borne in mind in kidney cases which exhibit a caudal position of the kidneys and abdominal pain or tenderness.

2. The transperitoneal operation is the operation of choice in dealing with horseshoe kidney.

3. If a horseshoe kidney is encountered upon lumbar operation and moderate efforts fail to dislocate it, it is advisable to defer further efforts rather than to make an enlarged and mutilating incision.

INFECTION OF THE KIDNEYS FOLLOWING PROSTATECTOMY.

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WHILE measures have been taken in recent years in the preparation and after-treatment of prostatics, tending to prevent uremia and hemorrhage, no special emphasis has been placed upon infection as a cause of death. Almost all cases of hypertrophy of the prostate suffering with urinary retention have an infected bladder. In case of immediate prostatectomy the infection is very liable to spread to other parts of the body and most frequently it ascends to the kidneys producing a pyelonephritis. There is a certain important group of cases, however, in which the urine is clear and sparkling, with no infection of the bladder and with only a small amount of retention, and it is in just these cases that a complete prostatectomy, done in one stage, may result in death. Even though the bladder is not infected at the time of operation it readily becomes infected when it is opened and pyelonephritis may be the fatal outcome. The raw, torn area from which the prostate is removed offers a most favorable area for absorption, for the entrance of microorganisms into the circulation and for the spread of an ascending infection to the kidneys.

The dangers following the operation of prostatectomy, named in the order of their occurrence, are said to be shock, toxemia, hemorrhage, uremia and later possibly pulmonary complications. Of these dangers uremia is said to be the most frequent cause of death, with hemorrhage as a close second. Symptoms of impaired kidney function called uremia clinically are said to produce about one-fourth of the deaths.

Uremia is not an exact diagnosis, and in most cases of so-called uremia following prostatectomy at autopsy a pyelonephritis is found. The various symptoms which manifest themselves in the clinical condition, however, may be dependent upon compensation of the cardiovascular system, and we are wont to associate it with the idea of a decreased amount of kidney cortex. Uremia due to a nephritis, in which the secreting cells of the kidneys are decreased and changed by an inflammatory and toxic increase of connective tissue, is not a frequent cause of death following prostatectomy. It is not always easy to distinguish clinically between uremia resulting from non-infective conditions as a cause of death and that due to a pyelonephritis and general infection. A patient may have a toxemia, be poorly nourished and secrete a urine of very low specific gravity, and death may ensue with the patient in a state of uremia. However, in such a case an infection may be the basic

cause and may be located in the kidneys in the form of a pyelitis or pyelonephritis.

In the consideration of the postmortem examinations that I have made on my cases at the Alexian Brothers' Hospital, St. Louis, following prostatectomy, infection in the form of a pyelonephritis has been a more frequent cause of death than any other factor. In those cases in which uremia has been a cause of death, clinically, a postmortem examination has shown the presence of an infection in the kidneys. The urinary bladder which has been infected in almost all cases of this type would seem to be the starting-point for the production of a pyelonephritis and septic infection.

Infection of the kidneys following prostatectomy is more frequently the cause of death than is at present considered to be the case. In my cases it has increased the mortality more than any other single factor. These patients suffering with prostatism are individuals advanced in age and in whom focal infection is very liable to be present in some distant parts of the body which may readily be lighted up by the weakened condition resulting from urinary retention and the following operative procedures: Infection of the kidneys may follow prostatectomy or may be present before the prostatectomy is done. Since catheterization of the ureters is difficult and cannot always be performed, very valuable information is given by a careful roentgen-ray examination. It is my custom to ray the kidneys as a routine measure, and with proper technic their form may be shown in every case. The best means of relieving infection of the urinary bladder is prolonged drainage. As a rule, when the patient fails to improve with free bladder drainage an infection in some other part of the body is present. An infection is most often located in the kidneys in these prostatics and is responsible for their failure to gain in strength. Whether or not preliminary cystotomy should be carried out I am of the opinion it should be done in all cases. A careful preparative period of a few months of the patient has gradually reduced the frequency of pyelonephritis and has lessened the mortality of operation. This preparation should also be directed toward resisting infection and continued as long as an infection remains.

Following the institution of free bladder drainage when the patient has improved as much as it is possible to make him improve, then the second stage of the prostatectomy should be carried out. It would also be reasonable to think that in a case of hypertrophy of the prostate, if the urine is clear and shows no pus and cultures show that the urine is sterile, the prostatectomy could be done in one stage, other things being equal. This is not true because it is in just these cases that the mortality is high in the one-stage operation. The urinary bladder in such a patient is called upon to resist an infection, when the patient has developed very little immunity, along with all the other dangers incident to the operation.

It is advisable to make cultures of the bladder urine in all cases of hypertrophy of the prostate. In those cases on the genito-urinary service at the Alexian Brothers' Hospital, St. Louis, in which a prostatectomy was done and an infection of the urinary bladder was present, the microorganisms isolated by culture from the urine were the colon bacillus, streptococcus, and the staphylococcus. The urine has contained varying amounts of pus from a few cells to large quantities of thick, creamy pus. In making cultures from the urine of cases of hypertrophy of the prostate, even though it is clear and sparkling, the colon bacillus and staphylococcus may be found.

It is advisable to make a cystoscopic examination in every case before operation. This examination cannot be made at once, as preparatory treatment is necessary before it is undertaken. Most patients that enter the hospital suffer with urinary distress and retention of urine, and as catheterization may be very difficult or impossible, it is frequently necessary to make a suprapubic opening in order to relieve the retention of urine. Frequently patients have a severe cystitis with calculi, rendering the bladder difficult of distention for examination. The prostatic urethra does not readily admit the cystoscope in this condition. The cystoscope may be passed through the suprapubic opening, the bladder being filled with water, and valuable information may be obtained in this way. By means of this the condition of the bladder wall as regards inflammation or tumor is seen and also the presence of a stone in the bladder, which is quite common in patients who have led a catheter life, or the fact of the presence of any foreign body in the bladder is learned. Information as to the size of the gland and the condition of the vesical neck, as to whether or not a prostatic bar is present, or whether the neck is contracted, is gained. It shows the amount of trabeculations of the bladder and the presence of any diverticuli. A cystoscopic examination, therefore, may show the cause of the prostatism, of which the patient complains.

From the review of the cases on my service the necessity of free bladder drainage and the treatment of the resisting infection is apparent, and it would seem to be the most important factor in the preliminary preparation of the patient for prostatectomy. It is possible to carry this out in a fair proportion of cases by means of systematic catheterization or by means of the retained catheter, but drainage of the bladder in this manner is not as perfect and does not give as good results as with a suprapubic cystotomy. There were a large number of cases in which the catheterization could be performed only with great difficulty. In all of my cases in which a retention catheter was used it was not borne well. In all badly infected cases the infection clears up more slowly, and such patients do not get along as well as when a suprapubic drainage is instituted. The patients that have gone to autopsy, when drained suprapubically were not drained for a very long period of time and the infection

still remained, or they have died from causes in no way dependent upon their urinary condition. Those patients that have recovered have been those that were drained for longer periods of time. Desperate cases in whom the preliminary suprapubic drainage was carried out at once, and the drainage continued for a month or longer, and in whom treatment for the existing infection was given have nearly always recovered.

Preliminary suprapubic drainage relieves the back pressure on the kidneys and permits a successful treatment of the infected bladder. In this way the absorption of the toxic products from the urinary bladder ceases and it is shown by the improved general condition of the patient. It is also seen in the decrease of the infection and by the diminution of the congestion and engorgement of the prostate gland. The gland becomes smaller in size as the infection clears up and its removal is made much more easy. The amount of bleeding during its enucleation is lessened and the raw, torn surface which remains after the removal of the gland is smaller than would ordinarily be the case. It follows, therefore, that the amount of absorption of toxic material following the operation is less than when a complete removal is done at once, when the prostate is of larger size.

Even though the urinary bladder is not infected and the urine is sterile to culture it becomes infected very soon after a suprapubic cystotomy is done. A prostatectomy done in one stage upon such a case may be followed by death and an autopsy shows a pyelonephritis to be the cause. Such a patient is called upon to resist infection at the same time with all the other factors incident to the operation. If in such a case the bladder be opened and free drainage instituted the individual has to combat only the infection which is acquired. A few weeks of free bladder drainage following the suprapubic cystotomy enables the patient to establish an immunity to infection by way of the urinary bladder. It is when this resistance has been established that the second stage of enucleation of the prostate may be carried out with little danger of a fatal infection of the kidneys resulting.

Hemorrhage following prostatectomy has been given considerable attention, and especially has it been emphasized as a cause of death. To control hemorrhage, Hagner has introduced a rubber bag. Kolischer has described the removal of the prostate through an incision after which he implants a piece of fat and sews up the incision to control hemorrhage, and many others emphasize the necessity of packing the cavity of the prostate with iodoform gauze. All of these measures have as their object the control of hemorrhage. It has been my custom in my work to give very little attention to hemorrhage. It has not been a cause of death in a single case. There is very little bleeding, especially if the patient has been given prolonged preparation for operation by drainage of the bladder for a long period of time. The anatomical conditions are such that there

are very few bloodvessels above where the enucleation of the prostate is begun and as the finger finds the proper line of cleavage, the lobes of the prostate are freed readily and the prostate is delivered with very little bleeding.

A study of the records of those cases in which a prostatectomy was done on the genito-urinary service of the Alexian Brothers' Hospital, St. Louis, and in which the cause of death was determined by a postmortem examination shows that an infection of the kidneys in the form of pyelonephritis was the most frequent cause of death. The greater number of deaths occurred when a complete prostatectomy was done in one stage. Death, however, has occurred following the first stage. The records for study may be classified as those cases in which death followed as a result of prostatectomy and those in which the fatal outcome was in no way dependent upon conditions due to operation.

An example of a case in which the patient had a clear sparkling urine, though with retention, and following a complete prostatectomy in one stage, death was caused by a pyelonephritis, is the following:

J. E. S., aged sixty-eight years, entered the Alexian Brothers' Hospital, December 30, 1918. On admission he had complete retention and a large prolapse of the rectum. Difficulty in urination for over two years has been present. He complained that urination was always prolonged, but there had never been any pain or burning. He had gradually been losing in weight but has had no previous urinary distress. On examination he was considerably emaciated. The prostate was very large, smooth and firm. He was given bladder irrigations daily and large quantities of nutritious fluids. A retention catheter was placed in the bladder but was not well borne. The following day on catheterization he had a residual of 100 c.c. The prolapsus had disappeared on systematic catheterization. The urine from the bladder was clear, sparkling and contained no pus, albumin nor casts. The general appearance and condition of the patient gradually improved. The phthalein output eight days after admission was 45 per cent. the first hour and 28 per cent. the second hour. The non-protein nitrogen was 65 per cent. per 100 c.c. of blood. His blood-pressure showed an average of 135 systolic and 95 diastolic. The leukocyte count was 8200. The total output of urine in twenty-four hours was 1800 c.c., with a specific gravity of 1.018. Nine days after admission the patient had 30 c.c. residual urine. He had improved in strength and apparently in resistance. He looked well and an examination of the heart and lungs was negative. On the eighth day the patient was given ether and the prostate was enucleated, the operation being done in one stage. The patient got along fairly well for four days following the operation, when his temperature suddenly rose to 105° F. and his pulse to 120. There was no pain present over the kidneys. The patient became uremic and hiccough developed. The tongue

was coated and dry. The skin was dry, the stupor increased and the patient became comatose and died the following day. At autopsy the anatomic diagnosis was: acute pyelonephritis, acute splenitis, acute degenerative myocarditis and edema of the lungs.

As an illustration of a case in which the patient had an infected bladder, with retention of urine and in which death was due to a pyelonephritis following a complete prostatectomy in one stage, I quote as follows:

C. B., aged eighty years, entered the Alexian Brothers' Hospital, St. Louis, May 2, 1919. On admission to the hospital he had a complete retention. A soft-rubber catheter was passed and 500 c.c. of cloudy purulent urine was evacuated. Patient has had difficulty in urination for the past three years and at five different times has had complete retention and had been relieved by catheterization. The last attack of complete retention was one month ago. Before these attacks of retention he had an attack of frequency and burning on urination. For the past three years the patient has had difficulty in breathing, and shortness of breath with pain in the region of the heart. Numerous hemorrhoids were present with a prolapsus ani. Irrigations of the bladder were instituted and a retention catheter was tied in. At the end of two weeks the patient had improved in appearance. The urine, however, still contained a large amount of pus. His combined phthalein output was 30 per cent. for the first hour and 12 per cent. for the second hour. The non-protein nitrogen was 120 per cent. for 100 c.c. of blood. The clinical diagnosis was hypertrophy of the prostate with retention of urine, cystitis with calculi of the urinary bladder, chronic myocarditis, pulmonary emphysema, chronic nephritis and cataract of the left eye. The patient had improved in appearance, and in strength, however, his retention of urine was complete. On leaving out the retention catheter he was unable to void. The improvement was such that prostatectomy in one stage was decided upon. The following day he was given ether and a complete prostatectomy in one stage performed. Following the operation the patient got along well. On the morning of the fourth day he developed a temperature which increased progressively, and by night was 105° F. He became dull, the tongue dry and he had a septic appearance. The leukocyte count was 12,000. A blood culture showed no microorganisms. Blood-pressure was 130 systolic and 90 diastolic. Pulse was 130 and full. The abdomen was soft and there was no pain or tenderness elicited by deep palpation over the kidneys. Death occurred the following day. The anatomic diagnosis was advanced pyelonephritis of both kidneys, acute splenitis and acute degenerative myocarditis.

It has been said that if a prostatic survives the preliminary operation of opening the bladder he will survive the second stage of removal of the prostate gland. This is not always the case. A

prostatic may die following the second stage of a two-stage prostatectomy from the usual cause of death, a pyelonephritis. This was true in a case in which the time of drainage of the bladder was short:

J. H. S., aged seventy-six years, was admitted to the Alexian Brothers' Hospital, April 6, 1920. On admittance to the hospital the patient was suffering with a complete retention of urine. He was in bad physical condition when admitted. Catheterization had been attempted repeatedly before admission and had failed, but in the hospital catheterization was successful and 500 c.c. of bloody, purulent urine was drawn off. The patient states that his urinary disturbance was of five years' duration and that this was his first attack of complete retention. He has suffered from shortness of breath and edema of the ankles at times. Examination showed a large smooth, boggy, movable prostate. With the exception of large hemorrhoids the rectum was free. Patient had a mitral insufficiency of moderate degree with an accentuation of the second aortic. He was uremic. The urine was scanty and contained albumin, pus cells and granular casts. He had edema of both legs and a cataract in both eyes. The clinical diagnosis on admission was retention of urine due to hypertrophy of prostate, chronic nephritis, mitral endocarditis, chronic myocarditis and cataract. The phthalein output was 22 per cent. for the first hour and 9 per cent. for the second hour. The non-protein nitrogen was 135 for 100 c.c. of blood. The catheter met a marked obstruction in the prostatic portion of the urethra and could only be passed with great difficulty, so that three days after admission a suprapubic cystotomy was performed under local anesthesia and a drainage tube was tied in place. A general improvement set in at once and twelve days following the suprapubic cystotomy the patient appeared to be in good condition. He had regained strength and resistance and looked well. A cystoscopic examination showed a moderate cystitis and a large bulging prostate within the bladder neck. A rectal examination showed the gland to be smaller and more firm than on admission. The urine still contained pus and a variety of microorganisms. The total urine in twenty-four hours was 1400 c.c. with a specific gravity of 1.016. The phthalein output for the first hour was 38 per cent. and for the second hour 18 per cent. The non-protein nitrogen was 120 per cent. per 100 c.c. of blood. The blood-pressure was on an average of 138 systolic and 90 diastolic. The temperature was normal. Edema of the legs had disappeared. Patient was able to walk about and did not remain in bed during the day. The examination of the heart and lungs showed pulmonary emphysema and mitral insufficiency, with arteriosclerosis, which were recognized on admission. On the twelfth day following the suprapubic cystotomy the patient was given ether and the prostate was enucleated. Following the second operation he did not do well. Four days later there was a sweet odor to the breath and he had

developed hiccough. His tongue was brown and dry and there was a tinge of icterus to the skin. Patient developed dyspnea. The temperature was 103° F. The following day the apex beat was diffuse and there was no muscular tone. The blood-pressure was 103 systolic and 104 diastolic. The temperature rose to 105° F., pulse to 138 and respiration to 50. The abdomen was lax. There was no tenderness present over the kidneys. The liver was not palpable. Symptoms gradually progressed and the patient died in coma. At autopsy the anatomic diagnosis was advanced pyelonephritis, acute myocarditis, acute bronchitis and chronic pulmonary emphysema.

A prostatic may also die following the second stage of a two-stage prostatectomy from a condition in no way dependent upon the operation.

An example of this is the following case:

L. B., aged seventy-eight years, admitted to the Alexian Brothers' Hospital, St. Louis, June 23, 1918. At the time of admission to the hospital he had complete retention of urine and was in a semi-comatose condition. Catheterization yielded 600 c.c. of bloody purulent urine. Examination showed a large, soft, prostate which was not fixed. Hemorrhoids were present. Patient was emaciated. The chest was barrel-shaped and a marked scoliosis was present. The specific gravity of the urine was 1.008 and numerous red blood corpuscles, pus cells and granular casts were present. The clinical diagnosis was hypertrophy of the prostate with retention of urine, chronic nephritis, chronic myocarditis, chronic bronchitis and arteriosclerosis. The retention catheter could not be kept in the bladder, so it was determined the following day to perform a suprapubic cystotomy in order to give free bladder drainage at once. This was done under local anesthesia and a large drainage tube was tied in. With free bladder drainage the patient rapidly improved and was able to give an accurate history of his condition. For over five years patient had returned to the hospital at various intervals with retention of urine. By systematic catheterization and bladder irrigations, patient had left each time feeling comfortable. Fourteen days following the first-stage operation patient had generally improved and was walking about. Cystoscopic examination at this time showed a large nodular prostate. The bladder showed numerous trabeculations. The urine from the bladder contained numerous microorganisms, pus cells and granular casts. Phthalein appeared in the urine after seventeen minutes. The total output the first hour was 32 per cent. and the second hour was 17 per cent. The non-protein nitrogen was 120 for 100 c.c. of blood. The blood-pressure was systolic 157 and diastolic 80. The total quantity of urine in twenty-four hours was 3700 c.c., with a specific gravity of 1.002. The leukocyte count was 10,400. The temperature was 98.6° F., respiration was 22. Patient had gained fifteen pounds

in weight. Fourteen days following the first stage operation he was given ether and the prostate enucleated. Within twenty minutes the patient had been returned to bed and was in excellent condition. On the fifth day following the operation the temperature and respiration were normal and the pulse was 110 and somewhat irregular. There was no hemorrhage; the urine was not bloody. The large suprapubic drainage tube had been removed and a smaller one had been instituted. The patient was rational. Respirations were thirty. There was a certain amount of dyspnea present. Twelve hours later the dyspnea was very great. The pulse was very rapid and thready. The apex-beat was diffuse and the patient had labored breathing. There was edema of the ankles present. Patient was given stimulation and water was increased as much as he would take. The dyspnea increased rapidly and the heart action became weaker and death occurred the following day. At the autopsy the diagnosis was mitral endocarditis with insufficiency. Chronic myocarditis, edema of both lungs, chronic passive congestion of the liver and spleen and chronic nephritis.

The case records which are quoted here are typical of their class and the autopsy findings are representative of what is found as a cause of death. No effort has been made to determine the mortality rate. The death-rate from prostatectomy has not been higher than with other individuals and institutions. More recently there have been fewer deaths, and I have attributed it to a better understanding of the presence of infection in the form of pyelonephritis which threatens prostatics, and to a prolonged, free, suprapubic drainage, and treatment for infection in their preparation for operation.

URINARY ANTISEPSIS: A STUDY OF THE ANTISEPTIC PROPERTIES AND THE RENAL EXCRETION OF 204 ANILIN DYES.¹

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OMAHA, NEB.

IN 1915 Hinman² pointed out the inefficiency of the several drugs at present in common use as urinary antiseptics and concluded that there is no known drug ideally suited for this purpose or even approaching the ideal. These observations are borne out by the experience of everyone who has had to deal with chronic infections of the urinary tract and also by the absence in the literature of conclusive experimental or clinical evidence of the fitness of any drug

¹ Investigations were carried on in the laboratory of the University of Nebraska College of Medicine, with the aid of an appropriation made by the United States Interdepartmental Social Hygiene Board.

² Urinary Antisepsis: A Clinical and Bacteriological Study, Jour. Am. Med. Assn., 1915, lxy, 1769.

for this purpose. The ideal internal urinary antiseptic should be chemically stable and relatively non-toxic and non-irritating; should be antiseptic in high dilution in urine as well as on agar (regardless of the reaction of the former), and should be eliminated in high percentage by the kidney without injury to the body. Clinically there is no such drug known.

For the purpose of urinary antiseptics, urotropin is the most widely used, and likewise the best suited available drug, on account of its well-known and proved action of liberating formalin in the urine. Urotropin, however, has very definite limitations, owing largely to the necessity for an acid urine for the liberation of formalin, and this becomes an insurmountable obstacle in those urines infected with alkalinizing organisms, such as the micrococcus urea or bacilli of the proteus group. As is well known, by the administration of acid sodium phosphate it is possible to cause a temporary slight increase in urinary acidity.

Henderson and Palmer³ have shown, however, that even after the administration of 10 grams of acid sodium phosphate at a single dose there follows only a slight increase in the hydrogen ion concentration, and in no case were they able to produce a urinary acidity greater than that which they had commonly observed in patients to whom no drug had been administered. On the other hand to produce and maintain a relatively large variation toward the alkaline end of the hydrogen ion scale, by the use of sodium bicarbonate, is comparatively simple. Therefore, granting that the efficiency of a given urinary antiseptic must necessarily be dependent upon the reaction of the urine, a drug efficient in alkaline urine only would be of greater practical value than is urotropin.

Another recognized limitation to urotropin is the time necessary for formalin liberation (Burnam⁴), which destroys the value of the drug at the kidney level and also in the bladder in cases in which for any reason there is rapid emptying or where a fistula exists. The main value of urotropin lies in its use as a prophylactic before instrumentation.

Summary of Previous Studies. Previous publications record the results of investigations with reference to the synthesis of an internal urinary antiseptic, carried on at the Brady Urological Institute, Johns Hopkins Hospital, in coöperation with Dr. Edwin C. White, chemist for that institution.* (Davis,⁵ Davis and White,⁶ Davis,

³ On the Extremes of Variation of the Concentration of Ionized Hydrogen in Human Urine, *Jour. Biol. Chem.*, 1913, xiv, 81.

⁴ An Experimental Investigation of the Value of Hexamethylenamin and Allied Compounds, *Arch. Int. Med.*, 1912, x, 324.

⁵ Urinary Antiseptics: A Study of the Antiseptic Properties and Renal Excretion of Compounds Related to Phenolsulphonephthalein: Preliminary Report, *Jour. Am. Med. Assn.*, 1918, lxx, 581.

⁶ Urinary Antiseptics: Further Studies of the Antiseptic Properties and Renal Excretion of Compounds Related to Phenolsulphonephthalein, *Jour. Urol.*, 1918, ii, 107.

White and Rosen⁷). Here an attempt was made to correlate chemical structure with the antiseptic properties and the renal excretion of the compounds studied, most of which were synthesized for this special purpose, with the hope that the introduction of certain groups into the molecule would produce certain desired properties. The study was limited largely to compounds related to phenolsulphonephthalein, because of the well-known extraordinary "renal affinity" possessed by this compound and because of its non-toxicity. Some interesting results were obtained which may be briefly summarized as follows:

1. It was possible to establish a certain relationship between chemical structure and renal excretion and to predict the excretion of molecules of certain structure, particularly those of the xanthone group. The halogenation of these compounds interfered with excretion.

2. Many of these compounds, non-toxic, excreted in the urine and antiseptic in water, lost this latter property when tested in voided urine.

3. One compound, chlor-mercury fluorescein, experimentally possessed all of the required properties, and when administered intravenously in minute dosage (5 mgm.) to dogs and rabbits caused the secretion of antiseptic urine for a definite period of time without injury to the animal.

Clinical investigation of this drug has not been carried out on account of its mercury content, although it was shown that in dogs the single lethal dose was forty times that necessary to cause the secretion of antiseptic urine. Chlor-mercury fluorescein, therefore, approaches the ideal in that (a) it is antiseptic in high dilution in either acid or alkaline urine; (b) it is excreted by the kidney with a rapidity as great as is phenolsulphonephthalein, and (c) experimentally efficient dosage may be administered without toxicity. Chlor-mercury fluorescein is an organomercury phthalein derivative in which the mercury is present in non-ionic form.

4. Continued experiments along the same lines (Davis and White⁸) have shown that acriflavin and proflavin are antiseptic in high dilution in urine (particularly in alkaline urine) and that intravenous administration of minute dosage (5 mgm. per kilo) to rabbits causes secretion of urine, which is antiseptic for a definite period of time without injury to the animal. Rabbit urine is normally usually alkaline. Failure to produce antiseptic urine in dogs with corresponding dosage of the same drug was probably due to the fact that dog urine is usually acid (average about p_{H} , 6).

⁷ Urinary Antisepsis: The Secretion of Antiseptic Urine Following the Intravenous Administration of an Organomercury Phthalein Derivative, *Jour. Urol.*, 1918, ii, 277.

⁸ Davis, E. G., and White, E. C.: Urinary Antisepsis: The Secretion of Antiseptic Urine Following the Intravenous Administration of Acriflavin and Proflavin, Preliminary Report, *Jour. Urol.*, 1918, ii, 299.

Possibilities Offered by Anilin Dyes. The following record summarizes the results of an investigation of the antiseptic properties and the renal excretion of 204 anilin dyes, the scope of the work being limited and guided, not by the chemical structure of these compounds but only by the number available. This investigation was carried on in the laboratories of the University of Nebraska College of Medicine with the aid of an appropriation made by the United States Interdepartmental Social Hygiene Board.

The anilin dyes were chosen for study (1) because of the large number of these compounds available, (2) because of their color and hence their ready detection and quantitative estimation in the urine and (3) because, through the work of many observers (notably, Churchman,⁹ Krumwiede and Pratt,¹⁰ Simon and Wood,¹¹ Kligler,¹² Graham-Smith¹³), the antiseptic properties of certain anilin dyes have become well known and therapeutic possibilities in this field have been indicated. Furthermore a consideration of the history of the development of the various tests of renal function (Thomas and Birdsall¹⁴) will call to mind that there are several dyes (fuchsin, rosanilin, indigo-carmin, uranin, trypan blue and others) which have been used to measure the functional activity of the kidneys, and which are therefore known to be excreted without injury to the patient. The staining and penetrating properties possessed by many anilin dyes likewise suggest suitability of this type of compound for medication of the urethral mucosa. This investigation was not undertaken without due realization of the handicap presented by impurities in commercial samples of anilin dyes.

Method of Investigation. Considering the large number of dyes to be studied it was advisable to select a few by preliminary test on agar, thus ruling out many as being unworthy of further investigation. The remaining few were then studied in regard to their antiseptic value in urine, their toxicity, their renal excretion and in regard to their ability to cause the secretion of antiseptic urine following intravenous administration. Finally, those few which were found to be particularly efficient against the staphylococci were tested on special media against the gonococcus. (Tables showing results with the gonococcus will appear in a subsequent publication.) The investigation was therefore divided into five stages as follows:

⁹ The Specific Antiseptic Action of Gentian Violet Corresponding to Gram, *Jour. Exper. Med.*, 1912, xvi, 221, 822.

¹⁰ Observations on the Growth of Bacteria on Media Containing Various Anilin Dyes, *Jour. Exp. Med.*, 1914, xix, 20 and 501.

¹¹ The Inhibitory Action of Certain Anilin Dyes upon Bacterial Development, *AM. JOUR. MED. SC.*, 1914, cxlvii, 247.

¹² A Study of the Antiseptic Properties of Certain Organic Compounds, *Jour. Exp. Med.*, 1918, xxvii, 463.

¹³ Some Factors Influencing the Actions of Dyes and Allied Compounds on Bacteria, *Jour. Hyg.*, 1919, xviii, 1.

¹⁴ Comparative Results of Various Functional Renal Tests, Based on a Series of Cases, *Jour. Am. Med. Assn.*, 1917, lxix, 1747.

1. *Antiseptic Values on Agar.* Determination of the antiseptic strength of the entire list of dyes on agar against *B. coli*, *Staphylococcus albus* and *Staphylococcus aureus*.

2. *Antiseptic Values in Urine.* Determination of antiseptic strength of selected dyes in both acid and alkaline urine against *B. coli*, *S. albus* and *S. aureus*.

3. *Toxicity and Excretion.* Determination of toxicity and renal excretion in rabbits of dyes shown to have antiseptic value in voided urine.

4. *Experimental Urinary Antisepsis.* Determination of the antiseptic value of the urine of rabbits which had received intravenous injections of dyes previously shown to be non-toxic and excreted.

5. *Inhibition of Gonococcus.* Determination on special media of the antiseptic strength against the gonococcus of those dyes which had been shown to inhibit the staphylococcus in high dilution.

1. *Antiseptic Values on Agar.* Preliminary antiseptic tests were carried out on the entire list of dyes, using agar neutral to phenolphthalein and of the following composition:

Agar	15 gm.
Peptone (Witte)	10 gm.
Meat extract (Liebig)	5 gm.
Sodium chloride	5 gm.
Water	1000 c.c.

Since the colon bacillus is by far the most frequent invader of the urinary tract, this organism was chosen together with *S. albus* and *S. aureus*. The agar was autoclaved in test-tubes in 9 c.c. amounts, after which 1 c.c. of an aqueous solution of the dye was added, the latter solution being at a concentration ten times that desired for the final dilution. Each dilution was then plated, cooled and inoculated by three parallel strokes from twenty-four-hour broth cultures of the three above-named organisms. No concentrations greater than 1 to 1000 were used, all dyes not showing antiseptic properties at this concentration being discarded. The selective antiseptic action against various organisms which Churchman has described, with particular reference to gentian violet, was exhibited by no less than 44 dyes, and in every case it was the colon bacillus that survived, while one or the other of the staphylococci (usually both) failed to grow. (See Figs. 1, 2 and 3.)

2. *Antiseptic Values in Urine.* As previous publications on this subject have indicated the possession of antiseptic properties by a drug when diluted in water or in agar is no indication whatever of its antiseptic value when diluted in urine. Many of the sulphonaphthaleins which were germicidal in high dilution in water lost this property when diluted in urine in a test-tube and even permitted the growth of organisms in urine when in relatively high concentration. In determining the antiseptic value in urine of the dyes selected by preliminary test on agar it was therefore desirable to

make the various dilutions with voided urine, since any drug for the above purpose would be useless unless effective in this medium. Furthermore, it was necessary to try out each dye in both acid and alkaline urines, since the ideal drug should be efficient regardless of the urinary reaction.

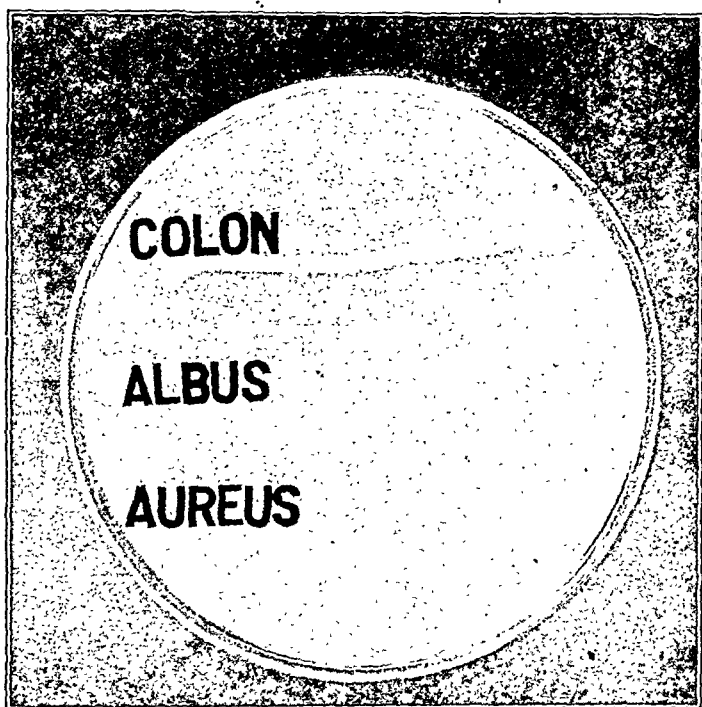


FIG. 1.—Photograph of agar plate containing chrysoidin-Y (1 to 1000), showing selective action of the dye in permitting growth of *Bacillus coli* and inhibiting *Staphylococcus albus* and *Staphylococcus aureus*.

In order to have available each day urine of definite acid and alkaline reaction it was necessary to titrate specimens of voided urine with tenth normal sodium hydroxide and tenth normal hydrochloric acid until definite degrees of hydrogen ion concentration were reached, as determined by the colorimetric method—that is, by comparison with a standard hydrogen ion scale made up with solutions of buffer salts colored by the sulphonephthalein series of indicators. (See publications of Clark and Lubs¹⁵ and Shohl and Janney.¹⁶) On the acid side of the scale it was arbitrarily decided to use urine titrated to p_h 6.4, which Henderson and Palmer have shown to be slightly less acid than the average reaction of normal urine. In

¹⁵ Colorimetric Determination of Hydrogen Ion Concentration, *Jour. Bacteriol.*, 1917, ii, 1.

¹⁶ Growth of *Bacillus Coli* in Urine at Varying Hydrogen Ion Concentrations, *Jour. Urol.*, 1917, i, 211.

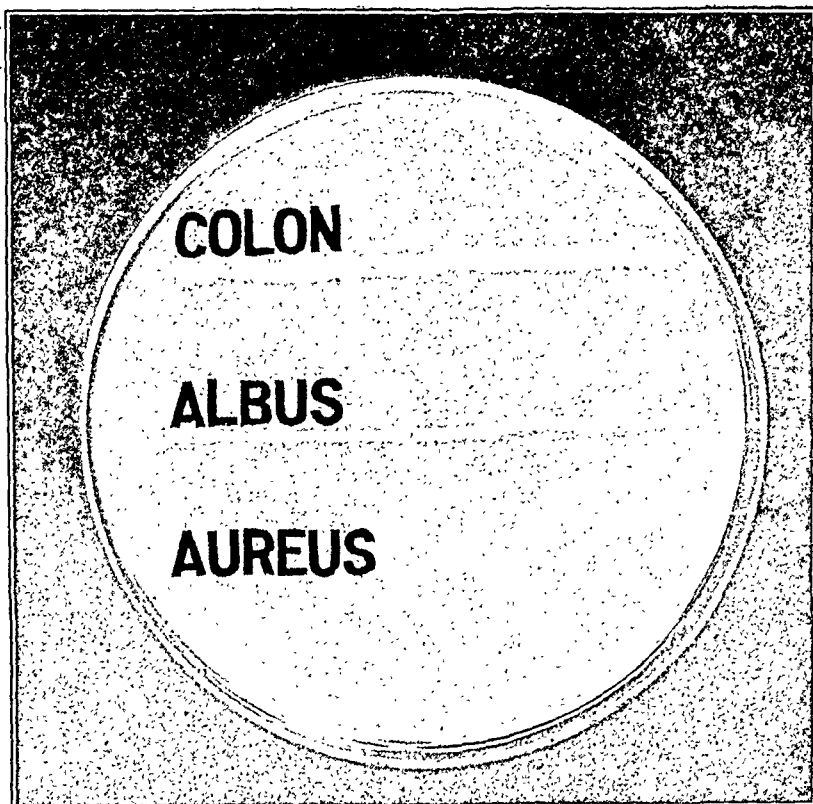


FIG. 2.—Photograph of agar plate containing phloxin-P (1 to 1000), showing selective action of the dye in permitting growth of *Bacillus coli* and *Staphylococcus albus* and inhibiting *Staphylococcus aureus*.

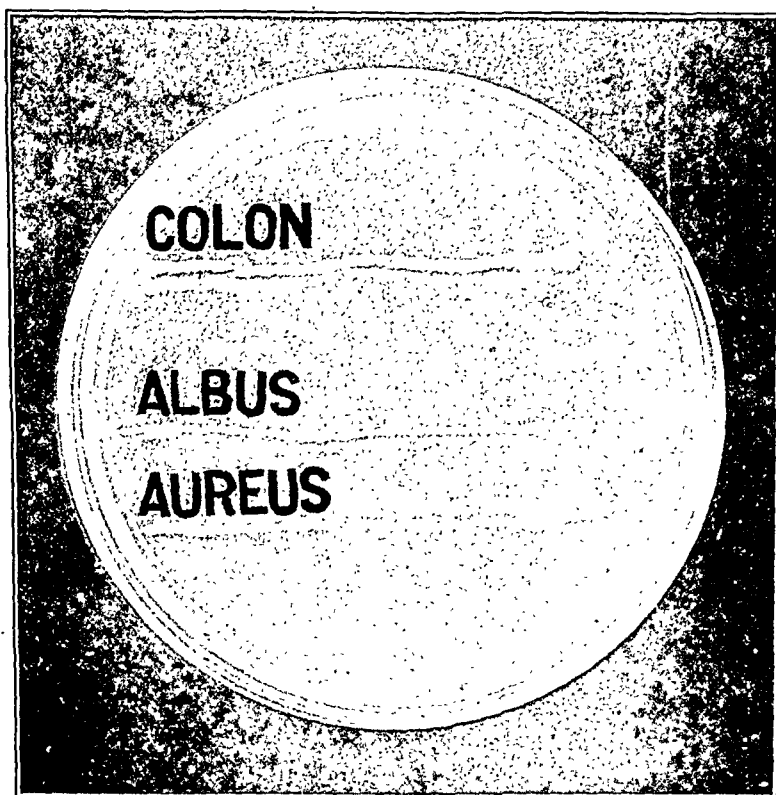


FIG. 3.—Photograph of control plate of drug-free agar, showing profuse growth of all three organisms.

order to obtain alkaline urine a sample of the same specimen was titrated to p_{H} 7.6, an end-point arbitrarily chosen so that the reaction of the specimens of urine used from day to day would not vary.

Dilutions of the dyes were made in sterile test-tubes, using acid urine for one series of dilutions and alkaline urine for another. Each dilution was inoculated with one loop of a twenty-four-hour

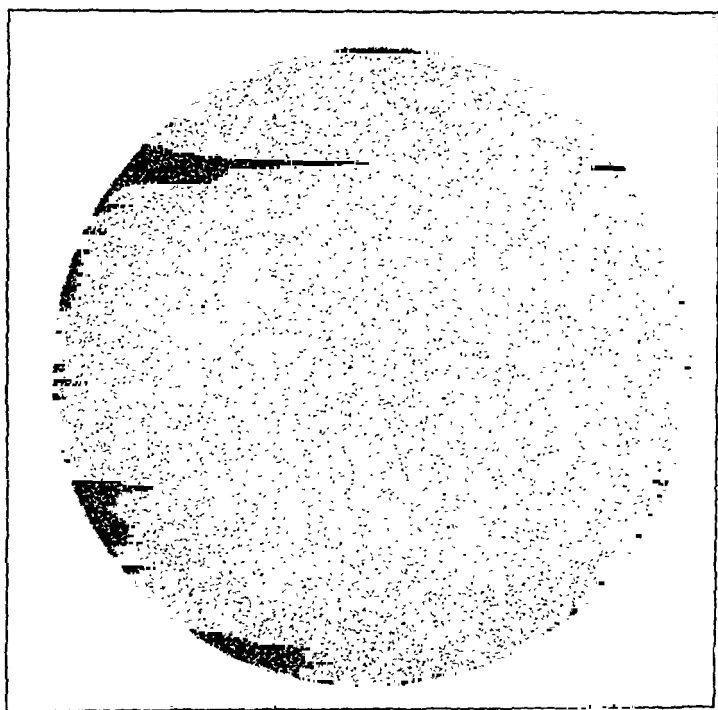


FIG. 4.—Photomicrograph (low power) of typical field in agar plate, showing absence of colonies and proving that the corresponding urine tube had contained a concentration of dye sufficient to kill the organisms during the twenty-four-hour incubation period.

broth culture of *Bacillus coli* in one series of experiments and with the *Staphylococcus albus* in another. After an incubation period of twenty-four hours (sufficient time to permit either growth or death of the organism), 0.1 c.c. was transferred from each tube to melted agar and plated. Those plates remaining sterile after incubation (Fig. 4) proved that the urine in the corresponding tubes had contained a concentration of the dye sufficient to kill the organisms within twenty-four hours. Those plates showing a few scattered colonies after incubation (Fig. 5) proved that the concentration of the dye in the urine had been sufficient to cause an arrest in the development of the organisms. This is the "bacteriostatic" action of antiseptics referred to by Hinman and should be

sufficient to control urinary infection provided the administration of the drug is continued. Finally, plates in which countless numbers of colonies developed (designated in the tables by the infinity sign ∞) proved that the concentration of the drug had been insufficient to prevent growth of the organism (Fig. 6).

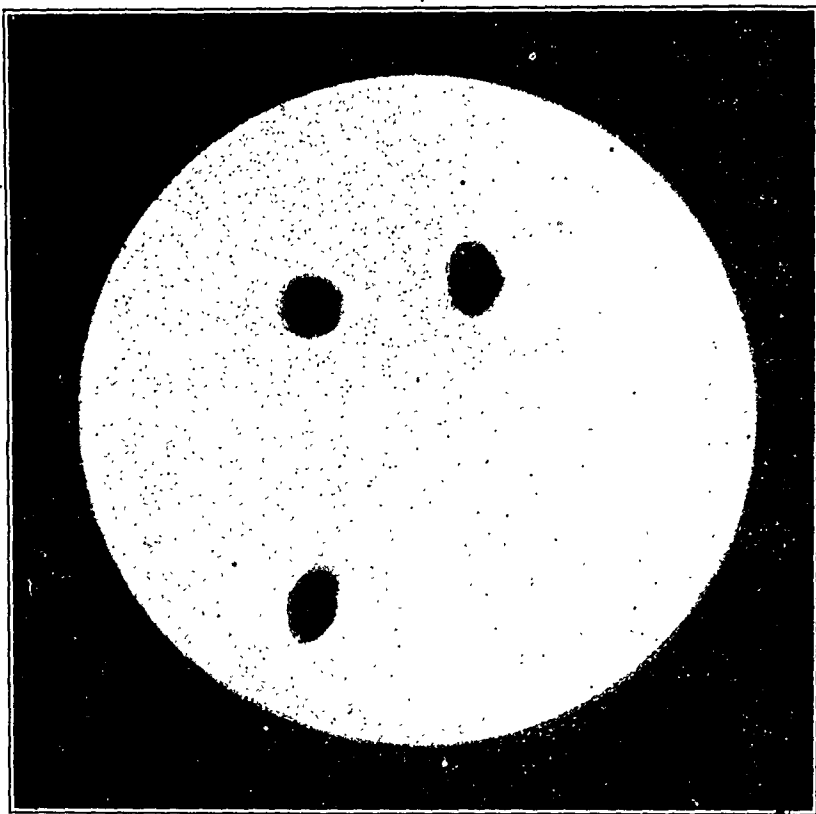


FIG. 5.—Photomicrograph (low power) of typical field in agar plate, showing a few scattered colonies and proving that the corresponding urine tube had contained an inhibitory or bacteriostatic concentration of the dye.

A consideration of Table II permits of several general conclusions. In keeping with the well-recognized clinical frequency of colon bacillus urinary infections, and with the stubbornness of such infections, is the hardness which this organism displays in urine *in vitro* in spite of the presence of antiseptic dyes. Out of a total of 204 dyes studied only 24 prevented the growth of the colon bacillus in urine in a dilution of 1 to 1000. Of these several were effective in alkaline urine only. A 1 to 1000 solution is a relatively high concentration, considering the extreme dilutions (several greater than 1 to 1,000,000) at which these same dyes are effective against staphylococci in the same media at the same reaction. Table II further shows that it is the general rule that these dyes are antiseptic in higher dilution in alkaline than acid urine. This fact might well prove to be of clinical importance, since the artificial production and maintenance of an alkaline urine is a relatively simple matter.

TABLE I.—RESULTS OF PRELIMINARY TESTS ON AGAR OF ANTI-SEPTIC VALUE OF THE ENTIRE LIST OF DYES AGAINST COLON BACILLUS (C), STAPHYLOCOCCUS ALBUS (Al) AND STAPHYLOCOCCUS AUREUS (Au). ALL DILUTIONS ARE 1 TO 1000. O = GROWTH. — = NO GROWTH.

Name.	No.	Antiseptic strength.			Name.	No.	Antiseptic strength.		
		C.	Al.	Au.			C.	Al.	Au.
NITROSO. Naphtholgreen B	4*	O	O	O					
NITRO Martius yellow	6	—	—	—	NITRO. Naphthol yellow S	7	O	O	O
STILBEN. Golden yellow	9	O	O	O					
PYRAZOLON. Flavazin L	19	O	O	O	PYRAZOLON. Tartrazin	23	O	O	O
Flavazin S	20	O	O	O					
Azo (MONOAZO). Chrysoidin Y	33	O	—	—	Azo (MONOAZO). Erika B extra	121	O	O	O
Chrysoidin R	34	O	—	—	Erika G extra	122	O	O	O
Soudan I	36	O	O	O	Victoria yel. O	134a	O	O	O
Ponceau 4 GB	37	O	O	O	Metanil yel. extra	134b	O	—	—
Orange G	38	O	O	O	Fast yellow	137	O	O	O
Chromotrope 2R	40	O	O	O	Brilliant yel. S.	142	O	O	O
Orange III	47	O	O	O	Chrysoin	143	O	O	—
Orseillier Mixt.	53	O	O	O	Orange I	144	O	O	O
Chrysoidin	69	O	O	O	Orange II	145	O	O	O
Brilliant orange O	70	O	O	O	Azofuchsin	146	O	O	O
Brilliant orange R	79a	O	O	O	Fast yellow	149	O	O	O
Brilliant orange R	79b	O	O	O	Orange T	151	O	O	O
Palatine scarlet A	81	O	O	O	Naphthyl amino br.	160	O	O	O
Ponceau R	82	O	O	O	Azo rubin	163	O	O	O
Ponceau 3R	83a	O	O	O	Fast red	160	O	O	O
Ponceau 3R	83b	O	O	O	Fast red D	168	O	O	O
Azoeosin G	94a	O	O	O	Cochénille red A	169	O	O	O
Azoeosin	94b	O	O	O	Fast brown 3B	172	O	O	O
Fast red	112	O	O	O					
Azo (DIAZO). Resorcin brown	211	O	O	O	Azo (DIAZO) Vesuvín B	284	O	O	O
Fast brown G	212	O	O	O	Azoalazarin Bord. W.	291	O	O	—
Fast brown	213	O	O	O	Brilliant yellow	303	O	O	O
Blue black	215	O	O	O	Benzopurpurin 4B	363	O	O	O
Palatine black	220	O	O	O	Benzopurpurin 6B	364	O	O	O
Brilliant crocein	227	O	O	O	Rosazurin	372	O	O	O
Soudan IV	232	O	O	O	Azo blue	377	O	O	O
Fast scarlet	248	O	O	O	Dianil blue B	380	O	O	O
Crocein scarlet	249	O	O	O	Trypanblue	391	O	O	O
Crocein scar, 7B	255	O	O	O	Chrysamin R	394	O	O	O
Bismark brown	283	O	—	—	Bavarian blue	450	O	—	—
AURAMINE. Auramine	493	—	—	—	AURAMINE Auramine G	494	O	—	—
TRIPHENYLMETHANE. Malachite green	495	—	—	—	TRIPHENYLMETHANE. Victoria blue 4R	522	O	—	—
Brilliant green	499	—	—	—	Fuchsin S	524	O	O	—
Lt. green SF bluish	504	O	O	O	Red violet 5RS	525	O	O	O
Lt. green SF yellowish	505	O	O	O	Acid violet 4BN	527	O	O	—
Erioglaucine A	506	O	O	O	Acid violet	529	O	O	O
Fuchsin	512	O	—	—	Formyl violet S4B	530	O	O	O
Red violet 5R ex.	514	—	—	—	Methyl blue	538	O	—	—
Methyl violet B	515	—	—	—	Soluble blue	539	O	O	O
Crystal violet	516	—	—	—	Amalgam green B	542	O	O	O
Methyl violet	517	—	—	—	Patent blue	543	O	O	O
Ethyl violet	518	—	—	—	Patent blue A	545	O	O	O
Methyl green	519	O	O	O	Cyanol extra	546	O	O	O
Aniline blue	521	O	O	O					

* Numbers correspond to Gustav Schultz, Farbstofftabellen, 1914 (5th edition).

TABLE I.—Continued.

Name.	No.	Antiseptic strength.			Name.	No.	Antiseptic strength.		
		C.	Al.	Au.			C.	Al.	Au.
DIPHENYLNAPHTHYL-METHANE.					DIPHENYLNAPHTHYL-METHANE.				
Victoria blue R	558	○	○	○	Wool green S	566	○	○	—
Victoria blue	559	○	—	—					
XANTHONE.					XANTHONE.				
Rodamine S	570	○	—	—	Eosin	587	○	○	○
Rodamine 6G extra	571	○	—	—	Methyleosin	588	○	—	—
Rodamine G extra	572	○	—	—	Eosin BN	590	○	○	○
Rodamine B	573	○	—	—	Erythrosin G	591	○	○	—
Rodamine 3G	576	○	—	—	Erythrosin	592	○	○	—
Sulphorodamine B	579	○	○	○	Phloxine P	593a	○	—	—
Fast acid violet B	580	○	○	○	Phloxine P	593b	○	○	—
Fast acid violet A2R	582	○	○	○	Phloxine	596	○	—	—
Acidrosamine	583	○	○	○	Rose bengale	597a	○	—	—
Fast acid blue	584	○	○	○	Rose bengale extra	597b	○	—	—
Chrysolin	586	○	○	—					
ACRIDINE.					ACRIDINE.				
Benzoflavine	605	○	—	—	Phosphine N	606b	○	—	—
Phosphine	606a	○	—	—	Rheonin	607	○	—	—
QUINOLINE.									
Quinoline yellow	612	○	○	○					
THIOBENZENYL.					Primuline	616	○	○	○
Thioflavine S	615a	○	○	○					
Thioflavine S	615b	○	○	○					
OXAZINE.					OXAZINE.				
Meldola's blue	649	—	—	—	Methylene blue	659	—	—	—
New blue B	650	—	—	—					
New methylene blue	651	○	—	—					
THIAZINE.									
Thiocarmine	662	○	○	○					
AZINE.					AZINE.				
Flavindulin O	668	—	—	—	Safranin MN	683b	○	—	—
Neutral red	670	○	○	○	Nigrosine	698	○	○	○
Indulin scarlet	671	○	—	—	Indulin NN	699	○	○	○
Safranin T	679	○	—	—	Indulin	700	○	○	○
Safranin OW	683a	○	—	—					
MISCELLANEOUS.					MISCELLANEOUS.				
Scarlet 6R	..	○	○	○	Pontacyl pr.	..	○	○	○
Diphenylamino orange	..	○	○	○	Congo red	..	○	○	○
Crystal scarlet	..	○	○	○	Scarlet B	..	○	○	○
Biebrich scarlet	..	○	○	○	Pontamine brown R	..	○	○	○
Croceine 3BX	..	○	○	○	Pontamine green GX	..	○	○	○
Guinea green	..	○	○	○	Pontamine green BX	..	○	○	○
Quinone	..	—	—	—	Pontamine black EX	..	○	○	○
Pontacyl sul. blue 5RX	..	○	○	○	Pontachrome yellow	..	○	○	○
Pontacyl ponceau	..	○	○	○	Pontamine orange	..	○	○	○
Pon. sul. acid blue R	..	○	○	○	Methylene blue ZX	..	—	—	—
Pontacyl azo flavine	..	○	○	○	Safranin T extra	..	○	—	—
Pon. sul. black 2B	..	○	○	—	Pontamine yel. SX	..	○	○	○
Pon. blue black SX	..	○	○	○	Primuline	..	○	○	○
Pontamine fast red F	..	○	○	○	Fast yellow NNX	..	○	○	○
Pontamine violet N	..	○	○	○	Erioglaucaine	..	○	○	○
Pontamine red B	..	○	○	○	Pontamine fast. yel.	..	○	○	○
Pontamine blue AX	..	○	○	○	Alkali blue	..	○	○	—
Pontamine sky blue 5B	..	○	○	○	Sulphogene ind. blue G	..	○	○	—
Pontamine purpur 10B	..	○	○	○	Aurine	..	○	○	—
Pontamine blue 2B	..	○	○	○	Sulphogene gr. G	..	○	○	—
Ponta. diazo bl. BH	..	○	○	○	Sulphogene or. L	..	○	○	○
Pontachrome black F	..	○	○	○	Thionol black XX	..	○	○	○
Pontachrome bl. 6BX	..	○	—	—	Sulphogene navy blue	..	○	○	○
Hydron blue G	..	○	○	○	Hydron blue R	..	○	○	○
Sulphogene Bordeaux B	..	○	○	○	Sulphogene br. G	..	○	○	○
Gentian violet	..	—	—	—					
STANDARD ANTISEPTICS.					STANDARD ANTISEPTICS.				
Mercuric chloride	..	—	—	—	Silver nitrate	..	—	—	—
Phenol	..	○	○	○	Ethyl alcohol	..	○	○	○

TABLE II.—DETERMINATION OF ANTISEPTIC STRENGTH OF BOTH ACID AND ALKALINE URINE OF 28 DYES SELECTED BY PRELIMINARY TEST ON AGAR FROM THE ORIGINAL 204, AS SHOWN IN TABLE I.

Group.	Dye.	No.	Antiseptic strength in urine.					
			Colon bacillus.			Staphylococcus albus.		
			Acid urine (pH. 6.4).		Alkaline urine (pH. 7.6).	Acid urine (pH. 6.4).		Alkaline urine (pH. 7.6).
			Inhibits devel.	Permits growth.		Inhibits devel.	Permits growth.	
Nitro	Martius yellow	6	1,000	10,000	1,000	10,000*	10,000*	10,000*
Azo	Chrysoidin Y	33	1,000*	10,000	1,000	10,000*	1,000	10,000*
	Chrysoidin R	34	1,000*	1,000	1,000	10,000*	50,000	10,000*
	Victoria yellow	134b	1,000	1,000	1,000	1,000	10,000	10,000
Auramine	Auramine	493	1,000	1,000	1,000*	1,000	10,000	10,000
	Auramine G	494	1,000	1,000	3,000	1,000	10,000	10,000
Triphenylmethano	Mal green	495	5,000*	1,000*	5,000*	900,000	1,000,000*	1,000,000*
	Brill. green	499	1,000*	1,000*	1,000*	900,000	900,000	1,000,000
	Fuchsin	512	1,000	1,000	1,000*	100,000	300,000	300,000
	Red viol. 5R ox.	514	1,000*	1,000	1,000*	100,000	300,000	700,000*
	Methyl viol. B	515	3,000	7,000	10,000*	100,000	300,000	1,000,000*
	Crystal viol.	516	1,000	3,000	10,000*	1,000,000*	1,000,000*	1,000,000*
	Methyl viol.	517	1,000	1,000	5,000*	3,000,000*	5,000,000	10,000,000
	Ethyl viol.	518	1,000	1,000	3,000	300,000*	500,000	1,000,000
	Victoria blue	522	1,000*	1,000	1,000	10,000*	900,000	900,000
	Rhod. 6G ox.	571	1,000	1,000	1,000	30,000*	70,000*	90,000
Xanthone	Rhod. 3G	576	1,000	1,000	3,000	100,000*	300,000	300,000
	Rose beng. ox.	597b	1,000	1,000	1,000	30,000*	50,000	10,000*
Acridin	Benzoflavine	605	1,000*	1,000	1,000*	10,000*	1,000,000	700,000*
	Rhocomin	607	1,000	1,000	1,000	10,000*	10,000	90,000*
Azine	Flavindulin	668	1,000	2,000	2,000	30,000*	70,000	50,000
	Indulin scar	671	1,000*	1,000	1,000*	900,000*	1,000,000	900,000
Miscellaneous	Saframin T	679	1,000	1,000	1,000	1,000	10,000	700,000*
	Saframin OW	683a	1,000	1,000	1,000	10,000	30,000	70,000
	Saframin MN	683b	1,000	1,000	1,000	10,000	30,000	300,000
	Acriflavine	...	5,000	7,000	100,000	75,000	100,000	200,000
	Saframin T ox.	...	1,000*	1,000	2,000*	100,000*	50,000	100,000
Standard antiseptics	Gentian violet	...	1,000	1,000	2,000*	100,000	900,000	900,000
	Phenol	...	1,000	1,000	1,000	1,000	1,000	1,000
	Hg. bichloride	...	10,000	30,000	30,000	10,000	30,000	30,000
	Ag. nitrate	...	10,000	30,000	10,000*	10,000	10,000	10,000*

* Indicates that plates showed a few scattered colonies, and that all the organisms were not killed, although there was distinct inhibition of development.

3. *Toxicity and Excretion.* Twenty-seven dyes were selected from Table II as seeming worthy of further study as to toxicity and excretion. Rabbits were given intravenous injections of from 5 to 25 mgm. per kilo and the urine collected at intervals and examined for the dye. Only in those cases in which the excretion was strikingly rapid and complete was an attempt at quantitative colorimetric estimation made. As shown in Table III, several dyes (malachite green, brilliant green, crystal violet, ethyl violet, victoria blue and others) were exceedingly toxic, causing convulsions and death within a few minutes. Autopsies showed a varying and bizarre selective distribution of the different dyes through the various tissues of the body. Several dyes (for instance chrysoidin R, crystal violet, rhodamin 3G, benzoflavin, indulin scarlet and others), though not fatal, were ruled out on account of hematuria or hemoglobinuria following minute dosage. Particular attention is called to the triphenylmethane group, of which many showed antiseptic properties in extreme dilution in urine. Dyes of this group, however, were also the most toxic, and those few which did not injure the rabbit failed to appear in the urine. (See Table III.)

TABLE III.—EXCRETION AND TOXICITY. RESULTS OF INTRAVENOUS INJECTIONS IN RABBITS OF DYES SHOWN IN TABLE II TO POSSESS ANTISEPTIC VALUE IN URINE.

Group.	Dye.	No.	Effect on animal.		Renal excretion.	
			Dose, mgm. per K.	Result.	Dose, mgm. per K.	Result.
Nitro . . .	Martius yellow	6	10	None	10	Moderate.
Azo . . .	Chrysoidin Y	33	20	None	20	Marked.
	Chrysoidin R	34	20	Hematuria	20	Moderate.
	Victoria yellow	134b	20	None	20	Moderate.
Auramine .	Auramine	493	10	None	10	Moderate.
	Auramine G	494	10	None	10	None.
Triphenyl- methane .	Malachite green	495	20	Lethal	4	None.
	Brilliant green	499	10	Lethal	4	None.
	Fuchsin	512	20	None	20	None.
	Red viol. 5R extra	514	20	Lethal	15	None.
	Methyl violet B	515	30	Anuria	20	None.
	Crystal violet	516	4	Hematuria*	4	None.
	Methyl violet	517	40	Lethal	20	None.
	Ethyl violet	518	20	Lethal	8	None.
	Victoria blue	522	8	Lethal	8	None.
Xanthone .	Rhod. 6G extra	571	20	Lethal	10	Moderate.
	Rhod. 3G	576	20	Hematuria	10	Moderate.
	Rose beng. extra	597b	20	None	20	None.
Acridin . .	Benzoflavine	605	10	Hematuria	4	Slight.
	Rheonin	607	20	None	20	None.
Azine . . .	Flavindulin	668	40	Lethal	20	Doubtful.
	Indulin scar.	671	10	Hematuria	10	Marked.
	Safranin T	679	20	None	20	Moderate.
	Safranin OW	683a	20	None	20	Marked.
	Safranin MN	683b	20	None	20	Marked.
Miscellaneous	Safranin T extra	...	30	None	20	Marked.
	Acriflavine	...	20	None	5	Marked.
	Proflavine	...	20	None	5	Marked.

* Hematuria lasted three days.

4. *Experimental Urinary Antisepsis.* Table III shows that of the total of 204 dyes studied there remained only 13 which were antiseptic in urine (*in vitro*), which were excreted by the kidney after intravenous administration and which exhibited no toxic properties following moderate dosage (about 20 mgm. per kilo). These dyes are listed in Table IV. It then remained to attempt to demonstrate antiseptic properties in the urine of rabbits following the intravenous administration of these drugs; that is, to determine whether passage through the blood stream and kidney would interfere with the antiseptic properties, and whether sufficient dosage could be safely administered to cause adequate concentration in the urine.

TABLE IV.—EXPERIMENTAL URINARY ANTISEPSIS. RESULTS OF ATTEMPTS TO CAUSE THE SECRETION OF ANTISEPTIC URINE BY THE INTRAVENOUS ADMINISTRATION TO RABBITS OF DYES, SHOWN IN TABLES II AND III TO BE ANTISEPTIC, EXCRETED AND RELATIVELY NON-TOXIC. C = COLON BACILLUS. AI = STAPHYLOCOCCUS ALBUS. ∞ = AN INFINITE NUMBER OF COLONIES. O = NO COLONIES.

Group.	Dye.	No.	Dose. mgm. per K.	Number of colonies which developed in in agar plate containing 0.1 c.c. of urine which had previously been inocu- lated and incubated twenty-four hours.							
				Urine obtained just before injection.		Urine obtained 2 hours after injection.		Urine obtained 6 hours after injection.		Urine obtained 12 hours after injection.	
				C.	AI.	C.	AI.	C.	AI.	C.	AI.
Nitro . . .	Martius yellow	6	10	∞	∞	∞	∞	∞	∞	∞	∞
Azo . . .	Chrysoidin Y	33	20	∞	∞	∞	∞	∞	∞	∞	∞
	Chrysoidin R	34	20	∞	∞	∞	∞	∞	∞	∞	∞
	Victoria yellow	134b	20	∞	∞	∞	∞	∞	∞	∞	∞
Auramine . .	Auramine	493	10	∞	∞	∞	∞	∞	∞	∞	∞
Xanthone . .	Rhod. 6G extra	571	10	∞	∞	∞	∞	∞	∞	∞	∞
	Rhod. 3G	576	10	∞	∞	∞	∞	∞	∞	∞	∞
Azine . . .	Flavindulin	668	20	∞	∞	∞	∞	∞	∞	∞	∞
	Indulin scar	671	4	∞	∞	∞	∞	∞	∞	∞	∞
	Safranin T	679	20	∞	∞	∞	∞	∞	∞	∞	∞
	Safranin OW	683a	20	∞	∞	∞	∞	∞	∞	∞	∞
	Safranin MN	683b	20	∞	∞	∞	∞	∞	∞	∞	∞
Miscellaneous	Safranin T extra	..	30	∞	∞	∞	∞	∞	∞	∞	∞
	Acriflavine	..	10	∞	∞	0	0	0	0	∞	∞
	Proflavine	..	10	∞	∞	0	0	0	0	∞	∞

In general the method of procedure was to compare the antiseptic properties of several specimens of urine, obtained by catheterization from a given rabbit before and at intervals of from one to several hours after drug administration. The necessity for a control urine has been pointed out in a previous publication (Davis and Hain¹⁷),

¹⁷ Urinary Antisepsis: The Antiseptic Properties of Normal Dog Urine, Jour. Urol., 1918, ii, 309.

which shows that normal dog and rabbit urine, for undetermined reasons, may occasionally act as an unfavorable culture medium for the colon bacillus and may even kill this organism after several hours. Each experiment was therefore accurately controlled by a specimen of urine obtained just before administration of the drug and inoculated and subjected to identically the same conditions as those specimens obtained at intervals after injection.

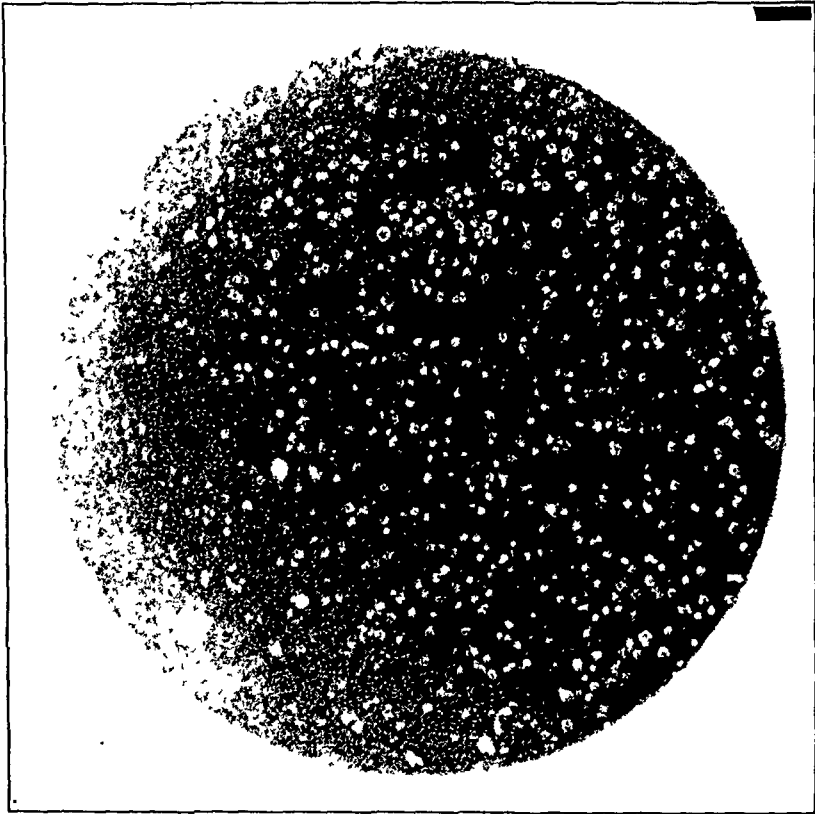


FIG. 6.—Photomicrograph (low power) of typical field in agar plate, showing a countless number of colonies and proving that the corresponding urine tube had contained an insufficient concentration of dye to prevent growth of the organism. The number of colonies in such a plate is designated in Table IV by the infinity sign ∞ .

Two samples (1 c.c. each) were transferred from each specimen of urine to sterile test-tubes, inoculated with *B. coli* and *S. albus* respectively (one loop of a twenty-four-hour broth culture) and incubated twenty-four hours, after which 0.1 c.c. was transferred from each tube to melted agar and plated. This technic was identical with that described in a preceding paragraph for determining the antiseptic properties of the same dyes in voided human urine, with the exception that the dyes were not added to the urine but were excreted by the kidney. The plates were inspected after forty-eight hours. A plate showing no colonies (Fig. 4) or

very few colonies (Fig. 5) proved that particular specimen of urine to be antiseptic, while the presence of countless numbers of colonies (illustrated by Fig. 6 and designated in Table IV by the infinity sign ∞) proved that the organism had grown and developed and that the urine had acted as a favorable culture medium. This method, dependent upon observing the number of colonies in an agar plate, accurately determines whether the organism has developed or died during the incubation period and is not open to fallacy, as is the method dependent upon gross inspection of incubated urine.

Table IV summarizes the results of attempts to demonstrate antiseptic properties in rabbit urine following the intravenous administration of the 13 dyes shown by previous selection (Tables I, II and III) to be antiseptic, excreted and non-toxic in moderate dosage. The same table shows the results of similar experiments carried out with proflavine and acriflavine. As a previous publication has pointed out (Davis and White⁸), and as the above experiments verify, proflavin and acriflavin are experimentally successful in that antiseptic properties in the urine may be definitely demonstrated following intravenous administration. (The flavins giving these results were manufactured by the Boots Pure Drug Company, Nottingham, England.) Out of the entire list of 204 new dyes, however, although preliminary experiment justified the final selection of thirteen, the properties of which indicated their possible value as internal urinary antiseptics, with none excepting proflavin and acriflavin, was it possible to cause the secretion of antiseptic urine by intravenous administration. In spite of the fact that these several selected dyes approached the ideal requirements (that is were antiseptic in urine, were excreted by the kidney and were relatively non-toxic), yet they failed at the final test when passed through the blood stream and kidney.

Conclusions.—1. There is no known drug ideally suited for the purpose of internal urinary antiseptics.

2. Of a total of 204 anilin dyes investigated 61 were found to possess antiseptic properties in agar, and 28 of these were efficient as antiseptics when added to voided urine.

3. As regards selective action against various organisms, this property was exhibited by no less than 44 dyes, in every case the colon bacillus proving more resistant than the staphylococci. There were only 24 which inhibited the colon bacillus in urine in a dilution of 1 to 1000.

4. There was almost no exception to the rule that antiseptic action was exhibited in higher dilution in alkaline urine than in acid urine. Attention is therefore called to the fact that these dyes are most efficient in urine of a reaction which renders urotropin inert.

5. The azo dyes give no promise of value, since of 37 of this group studied only 3 possessed antiseptic properties, and these only to a slight degree.

6. Of the triphenylmethanes many were antiseptic in high dilution in urine (some in dilution greater than 1 to 1,000,000). Of these, however, all but one were toxic and none was excreted by the kidney. This group is, nevertheless, worthy of further investigation.

7. Of 21 dyes of the xanthane group 3 were antiseptic in voided urine, and 2 of these were excreted to a moderate degree.

8. Of 4 acridine dyes 2 were antiseptic in urine. Neither was excreted.

9. Of 9 dyes of the azine group 5 were antiseptic in urine, and 3 of these (Safranin T, Safranin OW, Safranin MN) were excreted by the kidney with great rapidity and completeness and were non-toxic in 20 mgm. per kilo dosage.

10. By a study of 204 anilin dyes, chosen at random, it has been possible to select 15 which are (a) antiseptic in urine, (b) excreted by the kidney and which are (c) relatively non-toxic. With only two of these, however (proflavin and acriflavin) was it possible to demonstrate the secretion of antiseptic urine following intravenous administration.⁸

11. Considering that rapid renal elimination of anilin dyes is not unusual; that there are not a few dyes, relatively non-toxic, which exert a bacteriostatic action when diluted to infinitesimal amounts in voided urine; and that out of 204 dyes it has been possible to select 15 which approach the ideal and 2 which are experimentally effective; it is within reasonable expectation that a dye clinically suited for use as an internal urinary antiseptic may be discovered or synthesized. Experiments to date indicate that dyes of the triphenylmethane, xanthone, acridin and azin groups (particularly the latter) give more promise of value.

THE FOURTH VENEREAL DISEASE, ULCERATIVE AND GANGRENOUS BALANOPOSTHITIS: WITH CASE REPORT.

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JUDGING by the dearth of case reports and the rare mention of the so-called "Fourth Venereal Disease," it would seem that the existence of this condition is not a matter of common knowledge among physicians. Since Corbus and Harris¹ first called it to the attention of the profession in this country in 1909 but two others have made case reports in the American journals.^{2 3} Some of the

¹ Jour. Am. Med. Assn., May 8, 1909, lii, 1474.

² Bond, S. P.: Urol. and Cut. Rev., 1919, xxiii, 211.

³ Ross, C. F.: Virginia Med. Monthly, xlv, 36.

current text-books on urology make no mention of it while others merely give it passing notice. The article by Corbus in Cabot's recent treatise on *Urology* is quite complete, and by far the best that the author has encountered.

Frequency.—Were the disease extremely infrequent this lack of appreciation would be of no moment, but Bataille and Berdal,⁴ reporting 120 cases, state that it comprises from 2 to 3 per cent. of cases seen at l'hôpital du Midi. Sherber and Müller⁵ report 50 cases from Vienna seen in less than one year. Corbus⁶ says that it occurs infrequently in private practice—once in 200 cases—but is much more frequent in the clinics. He reports 7 cases in two contributions.

Definition.—The "Fourth Venereal Disease," or specific ulcerative and gangrenous balanoposthitis, is an acute inflammatory disease of the glans penis and opposed surface of the prepuce, characterized clinically by ulcerations and at times gangrene, accompanied by a copious flow of strongly odorous pus and caused by a spirochete in association with a fusiform bacillus. Constitutional symptoms are at times present.

History.—Previous to the work of Bataille and Berdal (1889-1891) several forms of balanoposthitis were recognized, including the ordinary form due to dirt, smegma, phimosis, etc., and some special forms, as the diabetic in which yeasts were found by Simon⁷ and the gonorrheal forms.

Ulceration and gangrene had been noted in cases of balanitis before this time but were not considered to constitute a disease entity.

Bataille and Berdal were the first to recognize in this condition a separate disease and to demonstrate its infectious, venereal, inoculable and auto-inoculable nature, and to describe its clinical aspects and etiology. They named it "Balanoposthite erosive circinée."

To demonstrate its inoculable nature they used humans, infecting them with pus from typical cases as follows:

(a) Pus was touched to a small incision on glans made by a scalpel.
(b) Pus was applied to the glans and prepuce after rough rubbing with a small stick.

(c) The inner surface of the prepuce was rubbed onto an ulcer of a case of this disease.

The results were positive in all three types of experiments. The disease was proved auto-inoculable by touching a freshly abraded spot on the glans or opposed preputial surface with pus from the same individual and securing the development of a new ulcer—thus

⁴ Mod. Méd., 1891, ii, 340, 380, 400, 413.

⁵ Arch. f. Dermat. u. Syph., 1905, lxxvii, 77.

⁶ Eros. and Gang. Balanitis, Jour. Am. Med. Assn., 1913, ix, 1769-1774.

⁷ Internat. Cong. Med., London, 1881.

simulating chancroid. There were no "takes" when these same tests were applied to the urethra or any surface other than that lining the preputial sac.

Etiology.—Bataille and Berdal ascribed the etiology to a spirochete which they found in nearly all cases, indistinguishable from that found in Vincent's angina, noma and mercurial stomatitis. No mention was made of the fusiform bacillus. Sherber and Müller⁵ and Corbus and Harris¹ not only found a similar spirochete but also a fusiform bacillus to a symbiosis of which they attributed the disease. The former writers were able to cultivate the bacillus, and in their first communication emphasized its importance over the spirochete. In a later paper (quoted from Corbus⁶), having failed to produce the disease by inoculation with this bacillus, they came to the conclusion that the spirochete plays the essential role in the etiology.

However, it may be that the bacillus and spirochete represent different morphologic types of the same organism, as seems to be the consensus of opinion regarding those found in Vincent's angina.

The vibrio is anaërobic, Gram-positive, $2\ \mu$ long by $8\ \mu$ wide, with pointed ends. It can be cultivated on serum agar.

The spirochete also is anaërobic, Gram-negative, 6 to $30\ \mu$ long by $2\ \mu$ wide. Its curves are not acute and its motility is great as observed in the dark field. The ends terminate in the center of the spiral.

As predisposing causes may be mentioned:

1. Redundant prepuce with a tendency to phimosis—favorable to anaërobic conditions.

2. Unclean preputial sac with its decomposing smegma.

According to Corbus⁶ unnatural sexual relations, or wetting the labia with saliva, is a predisposing cause, it having occurred in all of his cases. Opposed to this, however, is its absence or extreme rarity among high school boys in the masturbating age; the statement of Bataille and Berdal⁴ that women and women alone can give it, and the fact that Sherber and Müller⁵ do not mention it, at least in their first paper. It has still to be proved, too, that the organisms here are identical with those of Vincent's angina or the ordinary mouth spirochetes, although they are morphologically indistinguishable.

Pathology.—There are two forms of the disease, the ulcerative and the gangrenous, the latter being simply an advanced stage of the former.

Ulcerative Form. Exfoliation of epithelium occurs in numerous spots on the surface lining the preputial sac and preputial meatus. Progression leads to ulcerations which are irregular in outline, of a somewhat punched-out appearance, bright red in color, with a whitish margin of necrosed epithelium. Later the ulcerations become quite deep and are covered by a grayish-white mem-

brane which discharges much pus of a characteristic foul odor and yellowish-white appearance.

Microscopically there is infiltration by leukocytes, injection of vessels and exudation of serum. The spirochetes and fusiform bacilli penetrate the tissues even to the lumen of the bloodvessels and neighboring lymph nodes (Sherber and Müller).⁵

Gangrenous Form. Here the process continues to the stage of mortification, sometimes affecting the whole penis and necessitating amputation.

Symptomatology.—The period of incubation ranges from two to eight days. Subjectively, at first, there is mild itching, followed later by constant burning pain in the preputial sac, and extreme tenderness of the penis to manipulation. Pain on urination is characteristically absent at first, and when present later is due to urine in the preputial sac bathing the ulcers.

Objectively at first one sees the exfoliations followed soon by ulcerations and pus, etc., as described under pathology, the favorite sites being the sulcus, prepuce and glans in the order named. Edema of the whole penis, phimosis with heat and redness and palpable dorsal lymph vessel are common. Bilateral inguinal adenitis of an indurative character is frequent, but the nodes do not suppurate nor cause much discomfort.

Constitutional symptoms are absent in the mild cases, but prostration, fever, vomiting, etc., come on in more advanced ones.

The course of the disease is progressive to gangrene in cases with marked phimosis unless proper treatment is instituted, but may subside spontaneously when there is no such phimosis if the patient employs the ordinary methods of cleanliness. With proper care the cases are usually cured in two or three weeks.

The disease is sometimes complicated by the simultaneous presence of syphilis.

Diagnosis.—This is finally clinched by finding the characteristic vibrio and spirochete in the pus. While spirochetes are frequently found in the normal preputial sac, sometimes morphologically identical with those under discussion, the vibrio is never present (Sherber and Müller)⁶ and the combination of the two is pathognomonic.

Differentiation is to be made from chancroid, chancre, gonorrhea, herpes preputialis, venereal ulcer and ordinary balanitis. From a consideration of the known facts and characteristics of these diseases, together with microscopic examination, which after all is the means, *par excellence*, the diagnosis is easy.

Treatment.—Prophylactically, circumcision is of the greatest importance, since the organisms are anaërobic.

Cauterization, which might first come to mind, is contra-indicated not only because of the pain occasioned but also in that it renders anaërobic conditions possible beneath the coagulated albumin. The positive indications are to:

1. Treat the phimosis by a dorsal slit, thus aiding in the application of remedies and favoring aërobic conditions.

2. Irrigate the sac every few hours with peroxide of hydrogen solution.

3. Apply arsphenamin or neoarsphenamin daily to the ulcers in powdered form.

The following case, recently seen by me in consultation with Dr. George Fahr, illustrates a typical example except that the ulcers were confined to the prepuce.

CASE HISTORY.—A. B., a white male, aged twenty-six years, a University student, presented himself at the University clinic giving the history that eight days previously he had intercourse with a prostitute. Six days later he noticed itching and burning in the preputial sac, which was followed next day by a copious yellowish-white discharge of pus and much tenderness and swelling of the penis. There was no pain on urination. On examination the penis was red, tender and swollen and had a palpable dorsal lymph cord. There was a foul-smelling discharge of pus which on microscopic examination revealed the typical spirochetes and fusiform bacilli of this disease. Phimosis was present. Pain on manipulation of the part was severe. On clearing away the pus small ulcers were visible on the preputial meatus and the internal aspect of the prepuce. The glans was red but not ulcerated. The inguinal nodes were palpable, indurated and slightly tender.

The ulcers gradually deepened, new ones formed and some coalesced. Under a plan of treatment somewhat similar to that advocated in the body of this article there was complete recovery in less than three weeks. Unnatural intercourse was denied in this case.

AMNESIA AFTER CHILDBIRTH.

BY CHARLES W. BURR, M.D.,

PROFESSOR OF MENTAL DISEASES IN THE UNIVERSITY OF PENNSYLVANIA.

IN the first case, childbirth was the exciting cause of dementia with amnesia, in a woman strongly predisposed to insanity. The second illustrates a similar amnesia, resulting from an incidental complicating encephalitis occurring during pregnancy, in a woman free from pathological predisposition. In all other regards (the personality of the patients, their inheritances, the exciting cause of illness, and the accompanying symptoms) the two cases are unlike.

CASE I.—The patient's father was a man of unusual mental brilliancy, who, starting life with only a grammar-school education

and entirely without social influence, became not only wealthy, but, and this is more important, in judging mentality, a person whose opinions carried weight and who was respected in his community. He began when about thirty years old to drink heavily, not socially but secretly. In his earlier life he did not crave alcohol and drank rarely and moderately, yet he died a confirmed alcoholic, in his forty-fifth year, from cardio-vascular-renal disease. He was therefore not an accidental drunkard, made such by environment, but a man with congenitally tainted protoplasm, protoplasm having a pathologic affinity for alcohol. The patient's mother was very neurotic, given to outbursts of anger, hard to live with, unreasonable and always on the edge of insanity. She died at the age of thirty from some acute infection. She had several phantom pregnancies and three children, the first of whom died at birth, the second is a selfish, frivolous and not very intelligent young woman, and the third the subject of this report.

The patient was always "peculiar," but fond of music and outdoor life. She reached the second grade of a country high school at fifteen years, and then, being self-willed and under little control, informed her people she would not go to school any longer; she did not. As a child she never slept alone because of terrifying dreams, was bad-tempered, difficult, indeed impossible to train in self-control, but never physically ill. Menstruation began at fifteen years. (Probably mental unbalance, so frequent at puberty, was the real cause of her stopping school.) During adolescence she formed several transitory but violent attachments to boys, and by the time she was eighteen her sexual tendencies caused the wiser of the young men of her social circle, who were looking for wives, to avoid her. She married at twenty-two a foolish and infatuated youth, by whom she has had three children (all still living) in four years. Even before her attack of definite mental illness she was, though not a nymphomaniac, pathologically strongly sexed, entirely selfish, somewhat lacking in moral sense and with little intelligence.

In May, 1919, four weeks after the birth of her last child, who is claimed to be in good physical health, she suddenly became delusional, violent, suspicious of her husband, believed Christ was about to come again, masturbated frequently and slept but little. Six weeks after the onset of her illness, being left alone for a few minutes, she ran away and a few hours later was picked up in the street by the police, confused, erotic and exhibiting herself. She was taken to a hospital in a state of "acute mania," which lasted some days, after which she grew quieter but developed the delusion that she was the mother of Christ and at the same time stated she was going to marry a childhood friend whom she had not seen or heard of for years. (It is noteworthy that she had never received any religious training and never passed through any of the religious experiences common to adolescents, though in her father's family her forebears

had been strictly orthodox in belief and conduct.) Her husband, whom she still recognized, she accused of infidelity and would have nothing to do with. She was talkative, playful, impulsive, noisy, shameless, dirty and destructive. Very early in her illness she began to have recurring transitory visual and auditory hallucinations concerning religious and sexual matters, and throughout its course she wrote long, incoherent, obscene, profane and erotic letters. She gradually became quieter and after some months ate and slept well, was clean in her person, and, for the most part, quiet in her talk, though the erotic element still existed, because whenever she got even a glimpse of a man, no matter what his age, appearance, dress or race, she would call out to him and behave shamelessly. She masturbated much less frequently. Most of the time, except during the first months of her illness, she was emotionally apathetic, the sexual excitement being episodic, though even to the end she had occasional outbursts of apparently causeless anger.

The most interesting symptom was loss of memory or rather power of recollection. This loss especially concerned persons. She did not recognize her husband, treated him as she did all other men, but had no realization that she had ever seen him before. A relative who had taken care of her from infancy she did not recognize. Even seeing her children caused no emotional response and failed to awaken remembrance of them. For months she did not know where she was, and, though told repeatedly, always forgot in a few minutes. She retained ability to read and write throughout her illness, remembered the name of her home town, the place where she had lived as a girl and the memory loss involved not only events which had happened since her pregnancy; most of the incidents of her whole previous life were blotted out. For a long time also she had no idea of the passage of time; this really was the result of the memory loss; having no remembrance of what happened and was happening, she had no measure of time. During part of her illness she paid no attention to events happening around her: sometimes she was too maniacal, at others too apathetic, to do so. This period has remained a blank in her life. It really was not a memory loss, for memory is the permanent impress of stimuli upon the nerve cells and her nerve cells, for a reason unknown to us, refused to receive impressions. Mere lack of attention does not explain it because, as is well known, things we pay no attention to at the time may make their impress and be recollected long after.

For many months she responded normally only to the primitive instincts of hunger and sex, the latter being greatly exaggerated. When she had recovered enough to answer with verbal correctness when asked if she were married, she did not really understand what marriage connoted and did not think it strange she never saw her husband. She did not recognize him on the rare occasions when he was allowed to call on her and was not depressed by her separation

from her children. . She never spoke of them. During this period she had no intellectual life, never carried on a train of thought save when asked a question, was purely a creature of impulse, without power of inhibition, and had no continuing self-consciousness. She lived from moment to moment, without remembrance of the past or thought of the future. While she was under my care she showed no physical signs of disease except a pathologic growth of hair; some previously fine hairs on the chin and upper lip became coarse and marked. A few very coarse hairs also appeared on the cheeks in front of the ears. She presented no other visible evidence of endocrine gland dysfunction.

Convalescence was slow and the first real sign of improvement was the cessation of sexual excitement. (Though the religious delusions had passed away sometime before, they had been followed by so many other symptoms that their fading out was no indication of returning health.) Next she began to realize her loss of memory, at first without any emotional reaction, but later comprehending that she must be ill and worrying, though only slightly, about it. Power of recollection was one of the last functions to return, but the last of all, and it never has really returned, was affection for her husband and children. She even today has no affection, but merely animal feeling. After she recovered enough to understand intellectually what the words marriage and motherhood meant, she was still without the slightest affection for either husband or children. This lack of feeling toward her husband was not caused by her delusion of his infidelity (it had passed out of her mind long before) and persisted for many weeks after the entire period of her acute illness had become a blank in her life. Now, about thirteen months after the onset of her illness, she is able to live at home and to take nominal, not actual, charge of the house. Though to the careless observer she would seem to be a normal woman of a rather low mental type, she is, as a matter of fact, somewhat demented, as is shown by her indifference to her husband and children and her childish outlook on life. A large part of the time of her illness is a blank to her, though the power of recollecting events in her earlier life and incidents which occurred during her convalescence has largely returned. The amnesic period has not, however, clear-cut boundaries.

CASE II resembles the first in that amnesia was the great symptom. It is unlike in its causè (encephalitis) in the presence of a marked motor ataxia in both legs for many months, the absence of sexual symptoms, and in the patient's excellent ancestry, which gave her a protoplasm congenitally wholly normal. Her parents and grandparents, uncles and aunts were all, as I know from my personal knowledge, healthy mentally and physically. The patient's first pregnancy, which occurred in her twenty-sixth year, passed un-

eventfully; the child was normal at birth and remains so now, five years later. The second pregnancy occurred when she was twenty-eight years old; the child, a girl, was, I am told, physically healthy at birth, and so remains. During this pregnancy the mother had very severe morning vomiting, and just before the birth was seized with an illness which was diagnosed meningitis by the attending physician. She rapidly became palsied in both legs, and lost sight, speech and hearing. I suspect the alleged loss of sight was really photophobia and that the meningitis was really encephalitis (the cerebral type of infantile spinal palsy). She became delirious at the child's birth, and a week or ten days later, when the delirium cleared, recollection of past events was lost, not to be regained, even partially, for more than three years. When I saw her two years after the onset ataxia was so great in the legs she could neither stand nor walk, but there was no palsy; on the contrary, she could move the legs in bed strongly and with precision of movement. Striking the left patellar tendon caused adduction of the thigh, but no extensor movement of the leg, and striking the right caused adduction of both thighs. There was no ankle clonus and no plantar reflex. Sensibility to touch, pain and temperature was normal everywhere. There was marked general emaciation but no local trophic wasting, and no changes in the electric reactions of the muscles. Speech and swallowing were normal. The heart was normal, but the blood-pressure was only 100-70. There was a little incoördination in the left arm, but otherwise both arms were normal.

In addition to emotional indifference, and a loss of all sense of responsibility, the most marked mental symptom she presented, and her family told me it appeared immediately after the transitory delirium at the onset of her illness, was amnesia for events in her past life. She did not recognize any of her family, had no recollection of ever having been married or having born children (the second was born at the commencement of her illness), she did not know where she had lived, where she had gone to school, or what her previous life had been. On the other hand she retained her vocabulary, knew the meaning of words and talked sensibly. Her handwriting retained its former features. She remembered much of what she had learned at school, but almost none of the events of her school life, the friends she had made, and the like. She remembered how to sew. She had no delusions and her sense of sexual morality was strong, or rather it would be more accurate to say that she had no sexual feeling. Her manners were ladylike and her talk always clean. She (when under my care and for months previously) knew that there is such a thing as memory and that she had lost the faculty. At first she took this and her curious state of being the wife of a man whom she did not know with entire emotional apathy. Later it worried her greatly. She had no power of fixing anything in her memory. For example, if she started to read an article one

column long, in a paper, she would forget the first paragraph entirely before she reached the last. Things told or seen also made no impression. She conversed intelligently with me daily for months, and yet each day I was a new face, an unknown person. Later she almost suddenly regained the power of retaining and of recalling visual and auditory and indeed all stimuli. She then, of course, after once (in her new and normal state) seeing me, remembered me.

Almost three years after the onset she slowly regained ability to walk well. She has not as yet regained the power to recollect her past life save in a vague way, and one period is blotted out. Her natural feelings for her husband have returned, but whether it be a case of refalling in love or the return of an old love, who can tell? She does not remember her courtship and marriage nor the birth of her children. She recognized and remembered her mother and sister before she recalled her husband. She is now actually, not nominally, in charge of her home and has no dementia. Her judgment is good, and she behaves like a wise mother to her children.

Study of these two women reveals several interesting things. They illustrate the influence of heredity for good and evil. The first had a bad family history, was never really normal, and needed only the slightly added stress of several pregnancies in rapid succession to break entirely; the second, of good heredity, did not break from the stress of pregnancy but required a complicating infection (encephalitis) directly invading the brain, and, though amnesic, was not insane. Throughout her illness she retained what the insane, save the simple melancholiacs who are in a class by themselves, always lose, the moral sense.

Though we speak of the insanity of the puerperium there is no mental symptom or group of symptoms pathognomonic of pregnancy or childbirth, and almost every type of insanity may occur in association with childbearing. Even paresis, which is the one insanity having one cause and one only, syphilis, may have as its immediate occasion for appearing, pregnancy or more often, the act of birth. Childbirth almost always lights up a latent malaria, which sometimes is accompanied by a violent malarial delirium. Uterine sepsis also causes a delirium similar to that caused by fever from any cause. The most common true mental disease is a very acute confusional state.

Amnesia, except as a part of dementia, is rare and never occurs as an isolated symptom. Memory and recollection are not synonymous. Memory is passive—the permanent effect of a stimulus upon a cell. It is the unconscious storing of impressions in cells. Recollection is active: is the bringing anew into consciousness of the sensation, emotion or intellectual act caused by the original stimuli. Cells which have nothing to do with consciousness may be stored with memories and cells which have to do with consciousness may

also store memories which, though necessary to life, have no relation with consciousness. Again, certain memories must, at one stage of life, be recollected, be brought into consciousness, before a given act can be performed, while later all that need consciously be done is to will the act. For example a child learning to write must bring into the very center of consciousness the recollection of the muscular contractions needed to make each letter, while the ready penman is entirely unconscious of his muscular movements in writing: he simply orders the nerve-muscular apparatus to write, and it does so unconsciously. The same thing is true of walking, playing musical instruments and a thousand other acts. Probably every cell in the nervous system, if not every cell in the entire human organism, and indeed in all animal organisms, which performs any active function, is the seat of memories that though useful to life are never recollected, never come into consciousness. Muscle cells surely improve their function by practice, the result of unconscious memory. So do the cells having intellectual functions, and it is probable, certainly more than hypothetical, that all cells which secrete do the same. A few cells store no memories because they need none, having no active function, being mere bricks in the edifice, *e. g.*, those of bone, the crystalline lens and the outer layer of the epidermis.

Memory and recollection may be defective in several ways: I. Total permanent amnesia; *i. e.*, a complete and lasting loss of memory and power of recollection of all experiences. II. Partial amnesia, *i. e.*, loss of memory for a certain class of things, *e. g.*, amnesic aphasia and amnesic amusia (the loss of memory of the movements needed to be made to play a musical instrument). They are accompanied by word and music deafness. III. Amnesia covering only the events happening during a limited period of time, *e. g.*, just before an accident, before and after an epileptic fit or a period of delirium. IV. The amnesia accompanying alternating (double) personality, in which the patient at one time is one personality at another another, neither personality having knowledge or memory of the other. Though there are undoubtedly genuine cases of double personality, it is often pretended to be present by imaginative and histrionic ladies and gentlemen whose sense of fun, if not some more serious motive, leads them to hoodwink innocent and confiding gentlemen of science who, passing their lives in examining that always truthful witness, Nature, totally lack the useful scepticism of members of the defective force, and is today, since the condition is widely known, used by criminals of the higher class, who having disappeared and then been found, wish to give a good reason for their disappearance.

Total permanent amnesia, in the strict meaning of the word, never occurs save in the very last stages of dementia. The nearest approach to it is seen in paresis and senile dementia, but even in them some memories and some power of recollection are retained

until almost the last. The bed-ridden paretic, too demented to be delusional, showing no evidence of thinking, may yet prove by his behavior at eating time that he has a memory of certain favorite foods.

III is the type of amnesia most frequent after childbirth. Type I occurs in greater or less degree when a confusional state passes on to permanent dementia. II (amnestic aphasia) follows when a cerebral thrombosis involving the sensory speech centers occurs. It also may be transitory, in which case it probably is the result of local cortical poisoning.

Cases similar to those here reported are rare, but what percentage of pregnancies are followed by mental disorder remains unknown, because the published statistics are based on small series and on hospital cases only. For obvious reasons the women who go to maternity hospitals are more prone to complications than are those who are treated at home. The former, as a rule, have a poorer heredity and have had all their lives a poorer environment. Hence, hospital practice gives too high and private practice too low a percentage of mental disorders. The important element in prognosis as to future mental health in any pregnant woman, barring an accidental infection (such as Case II suffered), is her heredity.

REVIEWS

TREATMENT OF GONORRHEA. By NORMAN LUMB, O.B.E., Clinical Assistant to St. Peter's Hospital, London. Second edition. Pp. 120. Philadelphia: Lee & Febiger, 1920.

As a manual whose purpose it is to give to the general practitioner assuming charge of a "treatment center" (in England) a concise *resume* of this disease and its modern treatment this little book should meet a demand. It is of interest to find the author's faith and confidence in vaccine therapy, so little used in America, a method he employs routinely from the onset of the attack, and sustains its value from large army experience. We will not follow him, however, when he advises complete urethral lavage into the bladder in the beginning anterior urethritis—a method prone to spread infection that cannot appeal to any logical mind and a risk the author himself cautions against a few pages farther over. This is the only criticisable point found and is largely out-weighed by many commendable features that properly endeavor to lift the treatment of this communicable disease out of the rut of quackery and therapeutic desuetude on to a plane of scientific therapy.

A. R.

PUBLIC HEALTH AND HYGIENE. IN CONTRIBUTIONS BY EMINENT AUTHORITIES. Edited by WILLIAM HALLOCK PARK, M.D., Professor of Bacteriology and Hygiene in the University and Bellevue Hospital Medical College, and Director of the Bureau of Laboratories, Department of Health, New York City. Pp. 884; 123 illustrations. Philadelphia: Lea & Febiger, 1920.

BECAUSE of the great advances made in public health and hygiene in the past few years, this book comes at an opportune time. It contains much information of recent development. In this broad field no one individual could be proficient in all the ramifications of the subject, so very wisely the book is composed of a number of essays by writers who have had unusual experience in special branches. All has been collected under the editorial supervision of Dr. Park, who has himself written five chapters and one in collaboration on bacteriology and serology. The chapter on the prevention of infectious diseases is extremely valuable, because of the sugges-

tions for the control of the contagious, infectious and parasitic diseases. The knowledge obtained in the recent epidemics of pneumonia and influenza are presented here. The technic and application of the Schick test are given in a most practical way. Epidemiology is admirably outlined by Soper. Dodd discusses sanitary surveys. Winslow sets forth the needs and means of ventilation. Veiller writes interestingly on housing. Guerard elaborates on housing and plumbing as well as on soil and additional points on personal hygiene, while Fisk goes into the question of personal hygiene. Dunham discusses food and Atkinson the preservation and adulteration of food. Hess tells about vitamins. Bowles devotes a chapter each to water supplies and their purification and sewage and waste disposal. Mannheimer gives sanitation of swimming pools. Berry, military hygiene. Connor, tropical hygiene. Harris, individual hygiene. Baker, child hygiene. Bolduan discusses the sociologic and economic aspects of disease and public health education. Hoch, mental hygiene. Goddard, mental defectives. Cofer, maritime quarantine. Guilfooy and Wynne, vital statistics. Overton, rural public health work. The book should be well received by the medical profession and public health workers because of its thoroughness.

A. E. S.

OUTLINES OF INTERNAL MEDICINE FOR THE USE OF NURSES AND JUNIOR MEDICAL STUDENTS. By CLIFFORD BAILEY FARR, A.M., M.D. Professor of Gastro-enterology, Graduate School of Medicine and Associate in Medicine, Medical Department, University of Pennsylvania; Visiting Physician, Philadelphia Hospital for Contagious Diseases; Assistant Visiting Physician, Philadelphia General Hospital. Third and revised edition. Pp. 406; 70 engravings and 6 plates. Philadelphia and New York: Lea & Febiger, 1920.

THE third edition of this well-known member of "The Nurses Text-book Series" presents the same plan of subject treatment to be found in the preceding edition. Of the ten parts constituting the whole volume, eight are devoted to diseases of the various systems and two to harmful agencies (physical, chemical, bacterial), invading the body from without. The book is planned to supply the basis for a nurse's course in medicine and in addition to serve as a work of reference to which the nurse may turn for information.

It is a big question as to how much medicine should be taught to nurses in training. Undoubtedly an insufficient amount of information is dangerous. It would seem that the author of this work has incorporated just enough to make for adequately trained caretakers of the sick. Generally the medical courses offered to nurses have been of a desultory character.

Little exception can be taken to the information contained in the lines of this edition, inasmuch as it only touches on the fundamental and well-known principles of medicine. This is, of course, as it should be. The arrangement is well done and the index is sufficiently full for a reference work. T. G. S.

THE NEW PHYSIOLOGY IN SURGICAL AND GENERAL PRACTICE. By A. RENDLE SHORT, M.D., B.S., B.Sc. (LOND.), F. R. C. S. (ENG.), Examiner in Physiology for the F.R.C.S.; late Hunterian Professor, Royal College of Surgeons; Senior Assistant Surgeon, Bristol Royal Infirmary; Lecturer on Physiology, University of Bristol. Fourth edition. Pp. 291. New York: William Wood & Co., 1920.

IN 1911 the first edition of *The New Physiology in Medical and Surgical Practice* appeared. It evidently filled a need, for it has been reprinted several times and has now reached the fourth edition. The title is somewhat circumscribed and one must ask when *the* new physiology begins. In the opinion of the reviewer *the* could well be omitted. According to the author's statement in the first preface, "Many of the discoveries of the past ten years which have so changed the face of physiology are fraught with vast possibilities for the clinician;" while in this fourth edition he says that he has gathered the results of study, observation and experiment conducted during the last five years by Americans in research in pure physiology and British investigators devoting themselves especially to problems arising out of the material presented by the war. Therefore we interpret *new* to refer to the last two decades. The author attempts to sift out from this new physiology that which is likely to be of value in the actual diagnosis and treatment of patients.

Dr. Short has succeeded in presenting a most interesting and readable book with topics arranged by chapters in the following sequence: Food deficiency diseases; researches on blood, the heart, surgical shock; recent work on the functions of the stomach and intestines, the genital glands, the growth of bone, the thyroid and parathyroid glands, the pituitary and pineal glands, oxaluria, immediate and remote poisoning by chloroform, the functions of the spinal cord and peripheral nerves; localization of function in the brain; the action of cutaneous anesthetics and an appendix on the absorption of nitrogen from the amino-acids. At the close of each chapter abundant references give satisfactory suggestions for further reading, and an adequate index is among the valuable assets of the book.

There is sometimes disappointment in the lack of practical applica-

tion of results of experiments; perhaps this application of latent ideas is not too much to expect of the reader who is supposed to be "a general practitioner, consulting surgeon" or "candidate for the higher examinations in physiology." The absence of illustrations is noticeable and hardly compensated by a somewhat spectacular frontispiece. Undoubtedly frequent illustrations would be illuminating to those readers whom Dr. Short designates in the preface as "having the most elementary knowledge of physiology" and in consideration of whom "all technical terms have been avoided or defined."

DIABETES. By PHILIP HOROWITZ, M.D. Pp. 196; 27 illustrations; 2 plates. New York: Paul B. Hoeber, 1920.

DR. HOROWITZ has brought forth a little book on diabetes which has for its purpose the thorough correlation of the treatment between the patient and the doctor. The advice that he gives is sensible and practical and will give the patient a clear conception of the proper treatment of his condition, and give at the same time to the doctor a firm foundation upon which to base his treatment.

J. H. M., JR.

THE MEDICAL CLINICS OF NORTH AMERICA. Volume IV; Boston Number 2. Pp. 653; 59 illustrations. Philadelphia and London: W. B. Saunders Company, September, 1920.

THE first contribution of the *Medical Clinics* is that of Miss Ida M. Cannon, director of the social service department of the Massachusetts General Hospital and one of the leaders in this country in social service work. Her article is interesting and instructive, but it does seem that too great stress is placed upon the social factors in the management of these cases. For example, there is no doubt that social treatment is of great value in pernicious anemia. No one will gainsay that fact, but it is not the entire treatment of the condition, nor is it the most important treatment.

The next article, by Drs. White and Reid, is a very well-presented synopsis of the various physical findings in cases of mitral stenosis.

It would take too much space to mention in detail the seventeen other clinics which are incorporated in the present number of the *Medical Clinics*. It would not be amiss, however, to mention three of them which appear particularly helpful, dealing as they do with every-day medicine rather than with exceptional or unusual cases. Dr. White has a very comprehensive and thorough article on the modern examination of the stomach, while Dr. Ohler, in the

same careful manner, discusses the prognostic and diagnostic values of renal functional tests.

Lastly, Dr. Grover presents a really valuable discussion on the treatment of enuresis, one of the most difficult conditions with which the practitioner has to deal, unfortunately, as a rule, with poor results.

J. H. M., JR.

DIE TIERISCHEN PARASITEN DES MENSCHEN. By DR. MAX BRAUN, Professor at the University of Königsberg, and DR. OTTO SEIFERT, Professor at the University of Würzburg. Part II, Klinik und Therapie. By DR. SEIFERT. Second edition. Pp. 506; 19 illustrations. Leipzig: Curt Kabitzsch, 1920.

BRAUN'S *Tierischen Parasiten des Menschen* has long been a classic in the field of parasitology. The fourth edition of that work, appearing in 1907, contained chapters on the clinical application of parasitology by Prof. Seifert. In the last edition the clinical chapters have been expanded into a separate work, corresponding to the fifth edition (1915) of Braun's *Parasiten des Menschen*.

The present volume, then, does not treat of the parasites themselves but rather of the diseases that they produce, and these are discussed from the standpoints of distribution, pathological anatomy, symptomatology, and therapy. The chapters follow the natural divisions of parasites, and include amebæ, flagellates, trypanosomes, malaria, infusoria, the various classes of worms, arthropodes, and insects, but spirochetal diseases are omitted. The subject is handled in a somewhat unusual way, as the text consists of a summary of the work of individual observers all over the world; and authority is cited for almost every sentence, with full references in the footnotes at the bottom of each page. How skilfully this joiner's work must have been done will be evident when it is stated that the book is extremely readable and interesting. Indeed its peculiar value and unique position in the field of clinical parasitology depends on its full references to the literature. The author shows less than the usual German aversion to giving credit to foreign writers, though, since 1914, he has naturally not had very free access to foreign sources.

The usefulness of the book would have been greater if subheadings such as "Therapy," "Symptoms," etc., had been used, at least under the more important diseases. The quality of the paper is mediocre, but the type is very clear.

The book will be of first rate value to those doing special work on parasitic diseases, chiefly because of the excellent bibliography.

M. McC.

A TREATISE ON MATERIA MEDICA AND THERAPEUTICS, INCLUDING PHARMACY, DISPENSING PHARMACOLOGY AND ADMINISTRATION OF DRUGS. By the late RAKHALDAS GHOSH. Eighth edition, by B. H. DEARE, Lieut.-Colonel, Indian Medical Service, Officiating Principal and Professor of Medicine, Medical College of Bengal; Physician to the College Hospital; Dean of the Faculty of Medicine, University of Calcutta; and BIRENDRA NATH GHOSH, F.R.F.P.S. (Glas), Examiner in Pharmacology, University of Calcutta; Fellow of the Royal Society of Medicine; Joint Author, *A Treatise of Hygiene and Public Health*. Calcutta: Hilton & Co., 1920.

RAKHALDAS GHOSH was responsible for the first writing of this book. The title page of the present edition indicates that after his death its production has been entrusted to Lieut.-Colonel Deare and Birendra Nath Ghosh, both members of the Medical faculty of the University of Calcutta. This eighth edition is adapted to the new edition of the British Pharmacopeia.

The subject matter is treated in seven parts: *Materia medica* proper; pharmacy and dispensing; administration of drugs; pharmacology; *materia medica* and therapeutics; vaccine and serum therapeutics; and organotherapy.

In the present edition the drugs are arranged and classified according to their pharmacologic and therapeutic uses. This makes it an excellent book of reference for medical practitioners as well as students of *materia medica* and therapeutics. All of the information that one might wish to know about a drug is briefly given, including its source, characters, identification, incompatibles, composition, action, dose, pharmacology and therapeutics.

A complete index makes it a very admirable treatise, one, however, of more use to a Britisher than anyone else. T. G. S.

ELECTRIC IONIZATION: A PRACTICAL INTRODUCTION TO ITS USE IN MEDICINE AND SURGERY. By A. R. FRIEL, M.A., M.D. (DUB.), F.R.C.S.I.; Aural Specialist, Ministry of Pensions, London District; late Physician for the Throat, Nose and Ear, General Hospital Johannesburg; late Aural Surgeon and Bacteriologist, No. 1 South African General Hospital, B.E.F., France. New York: William Wood & Co., 1920.

"THE first chapter of this book explains what is meant by ionization and describes how the electric current can be utilized to introduce drugs into the affected parts of the body for the treatment of disease; the second deals with the equipment necessary and a short space is devoted to making clear some electrical terms; the third

chapter details the effects of different "ions" and the fourth gives an account of technic suitable for applying ionization to different parts of the body."

Fifteen diseases of the skin: suppuration of the eye, ear and nasal sinuses, pyorrhea, inflammations of the urethra and vagina and other conditions are said to yield to this method of therapy. In spite of the fact that the author in his introduction denies that the ionization method is a panacea, this list seems a rather large one to be influenced by a single means of therapeusis.

The subject matter is complete and well presented. The claims made for this method seem unusually wonderful. T. G. S.

THE X-RAY ATLAS OF THE SYSTEMIC ARTERIES OF THE BODY. By H. C. ORRIN, O.B.E., F.R.C.S., Ed. Fellow of Royal Society of Medicine, London; Civil Surgeon attached Third London General Hospital, R.A.M.C.(T.). Pp. 91; 21 plates. New York: William Wood & Co., 1920.

THIS atlas consists of a series of plates made from negatives of a full-time fetus whose arterial system had been injected with a substance opaque to the x-rays. Accompanying each illustration is an explanatory text. The systemic arteries show in continuity, each one being designated by a pointer, and their origin, course, anastomoses and bony relationship are easily studied. At the end of the atlas is a series of stereoscopic plates which aid materially in the study of the larger plates. As an aid to the student of anatomy, this handsomely illustrated volume adequately fulfills its purpose. J. D. Z.

A SHORT HISTORY OF NURSING. FROM THE EARLIEST TIMES TO THE PRESENT DAY. By LAVINIA L. DOCK, R.N., in Collaboration with ISABEL MAITLAND STEWART, A.M., R.N.; Assistant Professor, Department of Nursing and Health, Teachers' College, Columbia University, New York. London and New York: G. P. Putnam's Sons, The Knickerbocker Press, 1920.

THIS interesting book is a condensation of the four volumes of the larger *History of Nursing*, written by Miss Dock in collaboration with Miss Nutting. It is planned especially for the use of student nurses. Certain of the more recent developments in the nursing world not to be found in the more elaborate work are to be found in this new book. Much has been enacted in recent years by the white-capped profession, and that much is partly dealt with in

Chapter XII under the heading of certain aspects of nursing in the world war.

The authoresses begin with the things known about the care of the sick in the ancient world and in turn discuss Christian, aristocratic and military influence in nursing. The story of Florence Nightingale and her times is told in what must appeal to the reader as the most interesting chapter of the book. Nursing in America and the inspiring story of Clara Barton furnish the material for another splendid chapter.

The reading of this book should furnish to nurses an inspiration in the consciousness of being one part of a great profession—a profession rich in romance and adventure which links the past and present with a future of greater possibilities. The nurse who knows not of the history of nursing works partly in the dark. T. G. S.

HANDBOOK OF DISEASES OF THE NOSE, THROAT AND EAR. FOR STUDENTS AND PRACTITIONERS. By W. S. SYME, M.D., F.R.F.P. and S.G., F.R.S.E., Surgeon to the Ear, Nose and Throat Hospital, Glasgow. Pp. 329; 26 illustrations. Edinburgh: E. & S. Livingstone. New York: William Wood & Co., 1920.

THIS little book is of the type popular twenty years ago in America but now largely superceded by works of greater pretensions giving more detail to the subjects discussed, although not attempting the discussion of so many. It is the old "Manual" for students and general practitioners and in no way differs from many of its predecessors, even containing the familiar list of "formulae" at the end. Naturally enough in such a small volume the treatment of each subject must be most cursory and enough information is never given to enable anyone to care for a given and unfamiliar condition satisfactorily. For undergraduate students, perhaps, this work may be a guide and an index to classify for them the various diseases of the regions referred to and the outline of treatment given may answer the purpose. For post-graduate students or practitioners, it can have but little usefulness. G. M. C.

SOME CONCLUSIONS ON CANCER. By CHARLES CREIGHTON, M.D. Pp. 365; 114 illustrations. London: Williams & Norgate, 1920.

THE literature on the subject of cancer is ever increasing and were the amount of advance in our knowledge of malignancies commensurate with the increase in cancer literature, we should

be able to feel that we were approaching the goal toward which all eyes have been turned for many years, namely, the cause of cancer. The volume under consideration represents some conclusions of a man who has been more or less closely associated with cancer research for almost fifty years and who has a very broad knowledge of the literature, both past and present.

After a rather extensive introduction the author devotes the first section of his book to three types of malignancy which are used to illustrate principles. Thus, deciduoma malignum or chorionepithelioma represents a type in which a ferment action upon the blood reduces it to become a trophic substance so that blood-fed cells arise in the walls of the vessels and constitute one of the most malignant cancers known. In the second instance, mouse cancer is cited as a type of growth dependent upon a dyscrasic state of the blood due to excessive inbreeding. The third type described is the malignancy of the eyeball, supposedly due to the change of the cells which normally as a medium of nutrition into blood-feeding cells to a malignant end. The second part of the book is devoted to rather complete discussions of cancer as it occurs in various regions of the body. Frankly speaking, the book is not one that will appeal to the large majority of the profession as it is written by a laboratory man in laboratory language, hence it is unintelligible to the practical physician who has not been closely following cancer research. If it is the intention of the author to popularize his book, the reviewer would suggest a brief practical summary to each chapter so that the busy practitioner could get the conclusions quickly instead of being forced to read so many pages of obviously uninteresting theoretical considerations.

F. B. B.

MANUAL OF PEDIATRICS. FOR STUDENTS AND DOCTORS. By DR. WALTER BIRK, Professor of Pediatrics, University of Tübingen. Vol. II, 4th ed. Pp. 338; 10 illustrations. Bonn: A. Marcus & E. Weber, 1920.

VOLUME I, recently reviewed, was devoted to the diseases of infancy. Volume II takes up the diseases of the remainder of child life. Very properly the author begins this volume with a complete consideration of the diet, care and nutritional disorders of older children. Diseases of the gastro-intestinal tract and the abdominal viscera are discussed in short but clear paragraphs. The acute infectious diseases, the so-called diseases of childhood as well as such infectious diseases as typhoid fever, tuberculosis, acute rheumatic fever and syphilis receive deserved attention. The diseases, requiring amplification of discussion, receive it, while

less severe or important ones are discussed briefly but lucidly. Diseases of the air passages, of the heart, of the nervous system, of the genito-urinary apparatus and diseases of the blood are presented to the reader in a most satisfactory manner. In his preface Dr. Birk apologizes for the absence of a section on diseases of the skin, but as he treats these so efficiently under the general headings, a chapter would seem superfluous. As a whole, the book is very valuable to a physician, but because of its general avoidance of detail, it is probably less valuable to the medical student.

A. E. S.

PLASTIC SURGERY OF THE FACE. By H. D. GILLIES, C.B.E.; F.R.C.S., Major, R.A.M.C., Surgical Specialist to the Queen's Hospital, Sidcup, etc. Pp. 408; 844 illustrations. London: Oxford University Press, 1920.

AT no one hospital of any of the allied forces was there such a rich mass of clinical material, nor were better facilities provided for the care of war injuries of the maxillofacial region, than at the Queen's Hospital, Sidcup. It was at this hospital that several of the more important advances in plastic methods were worked out and developed by Gillies and his colleagues. Among these may be mentioned the "tubed" pedicle flap, original with Gillies, the free epidermic inlay graft for replacing lost mucous membrane of the mouth, the epidermic "outlay" for reconstruction of eyelids, recognition of the necessity for an epithelial lining for rhinoplastic flaps. The superiority of the type of work being done at Sidcup was recognized by Surgeon-General Gorgas, who early in 1918, obtained permission to detail a number of American Army surgeons and dental surgeons as observers, and the knowledge gained there played an important part later in the facial restorations done on our own men.

The first thirty-four pages of the book are occupied with a consideration of the principles adopted by the author in plastic surgery of the face. The first principles governing the whole treatment of facial injuries are, diagnosis of the tissues involved, and replacement of all tissues as early as possible into their normal positions. Some valuable points are given in the formation of flaps to close defects. The question of anesthesia for these cases is taken up by Captain R. Wade, who prefers intratracheal ether or chloroform and oxygen through a nasal tube.

The greater portion of the book takes up in detail the repair of injuries of the various portions of the maxillofacial area, and consists largely of a description of individual cases. Almost every conceivable form of facial injury and its treatment is described and depicted in the illustrations. The diagrams of the operations

are particularly instructive. For restoration of missing portions of the mandible the writer prefers a graft from the crest of the ilium. Where the loss of bone includes the whole of the ascending ramus Gillies uses a piece of the seventh or eighth rib taken from the opposite side, including the costochondral junction and some of the cartilage. The maximum point of convexity forms a new angle of the mandible, while the ascending ramus is represented by that portion of costal cartilage which runs upward to the sternum. A false joint in the neighborhood of the glenoid fossa is made in this way, and a cosmetic and functional result thus accrues. A very important chapter deals with the prosthetic appliances, made by the dental surgeon, for maintaining the hard tissues in their correct alignment and for replacing those parts which cannot be restored by plastic surgery. The more important of these appliances include splints for fixation of fracture of the jaws and for supporting epithelial inlays, obturators for closing defects of the palate, nasal splints with dental fixation, as a support in rhinoplasty. In rhinoplasty, the Italian and French methods are discarded, in favor of either the Indian method or the horizontal forehead flap with superficial temporal pedicle. The final chapter points out the application of the experience gained in war injuries to the repair of facial deformity due to disease or injury incurred in civil life.

The book is the most complete that has been written upon this subject and one which no surgeon can afford to be without.

R. H. I.

DISEASES OF THE INTESTINE AND LOWER ALIMENTARY TRACT.

By ANTHONY BASSLER, M.D., Professor of Gastro-enterology, Fordham University Medical College and New York Polyclinic Medical School and Hospital; Visiting Physician, New York Polyclinic Hospital; Visiting Gastro-enterologist, People Hospital. Pp. 660; 154 illustrations. Philadelphia: F. A. Davis Company, 1920.

DR. BASSLER has followed, most logically and successfully, his book on *Diseases of the Stomach and Upper Alimentary Tract* with the present work on *Diseases of the Intestines and the Lower Alimentary Tract*. However, the present addition to his published studies of the gastro-intestinal tract does not seem quite as thorough or carefully presented as his earlier book. Briefly, the first six chapters of the book deal with gastro-intestinal anatomy, physiology, chemistry, roentgenology, as well as the history and examination of the patient. The succeeding chapters deal with the various abnormal conditions within the intestinal tract as well as the pathological processes in the intestines themselves. Probably the most elaborate discussion is that which deals with the question

of intestinal toxemia. To this subject are assigned many pages filled with rather complicated suggestions as to diagnosis and treatment. It is certainly an open question as to the exact role which putrefaction within the intestinal tract plays in the production of symptoms, and while it may be conceded that it has such a role; nevertheless, it is impossible to concede rather didactic statements which attempt to demonstrate the existence of the various types of bacteria that are responsible for these symptoms, and to acknowledge that the symptoms can be cured by the production of vaccines prepared from these organisms. So little is definitely known about the life cycle, the type, the saprophytism, and so on of the bacteria of the small intestines, that treatment with vaccines does not seem to be the scientific method of treatment, to say the least. Furthermore, in the hands of Dr. Bassler, it might be possible, by bacterial methods, to isolate the offending organisms, but certainly, the technic, as the author gives it, is so difficult and so complicated that it would be utterly impossible for the average man to carry through, and this, in spite of the fact that the book is dedicated to the "practitioners of medicine, the best friends of the human race." While it is true that differences of opinion may exist between the author and reviewer, a natural result in discussing such a complicated subject as autointoxication, nevertheless the reviewer feels that in other respects the volume should prove of value to those who are interested in the subject of enterology as well as to those who are engaged in ordinary practice. It seems a pity that the subject of enteroptosis is not included in this book because it is such an important disorder, and those who do not possess the author's volume on *Diseases of the Stomach* will be without a discussion of this interesting protean subject.

J. H. M., JR.

A PRACTICAL MEDICAL DICTIONARY. By THOMAS LATHROP STEDMAN, A.M., M.D., Editor of the *Twentieth Century Practice of Medicine*, of the *Reference Handbook of the Medical Sciences*, and of the *Medical Record*. 6th revised edition. Pp. 1131. New York: William Wood & Company, 1920.

THE sixth edition of Dr. Stedman's medical dictionary has been amplified by a large number of new words and new definitions, making the volume some twenty pages larger than the preceding edition. The reviewer had the pleasure of reviewing the fourth edition of this work, and all that he said at that time in commendation of the fourth edition holds for the present edition. A dictionary seems like a very dry and uninteresting compilation of words and definitions, yet truly no form of literary work requires more the scholarly pen of one, who, like Dr. Stedman, is versed in all the sciences, from paleontology to philology, from psychology to syndesmology.

J. H. M., JR.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Heart and its Rhythm in Acute Rheumatism.—PARKINSON, GOSSE and GUNSON (*Quart. Jour. Med.*, 1920, xiii, No. 52, 363-379) recall the frequency of endocardial and myocardial disease initiated during an attack of acute rheumatism and the difficulties encountered in diagnosing the latter condition. Their investigation consisted in a search for signs indicating acute myocarditis and eventual myocardial disease likely to determine heart failure, in 50 cases of acute rheumatic fever. All other available physical signs were noted. The size of the heart, as indicated by the apex beat, varied but little and from their studies the authors conclude that the frequency and degree of enlargement of the heart during an attack of rheumatic fever have been exaggerated. No relationship was found between the development of systolic murmurs at the apex and demonstrable cardiac enlargement. Sinus arrhythmia was present after the attack in 47 cases (94 per cent.). It occurred in 2 cases with a pericardial rub, 1 case with a pericardial effusion, 1 after flutter and in each of 15 cases which had developed acute heart-block. They (authors) feel therefore that the presence of sinus arrhythmia does not indicate that the heart has escaped infection. Premature auricular contractions occurred in 7 cases (14 per cent.). Paroxysmal auricular flutter occurred in 1 of these. Auricular fibrillation did not occur during the disease in any of the cases. The authors conclude that auricular disease (such as fibrillation and flutter) is often the sequel of acute rheumatism; that the frequency of extrasystoles in this infection and their association with flutter and heart-block suggest that they indicate acute myocarditis. Some degree of auriculoventricular heart-block developed in 15 cases (30 per cent.). Of these 11 (22 per cent.) showed delayed conduction only, the

remaining 4 showed partial heart-block with dropped beats, and in 1 of them the degree of 2-1 heart-block. These phenomena invariably disappeared during convalescence. The observers conclude that heart-block is common in rheumatic fever; that it indicates acute myocarditis; that it may, therefore, be premonitory of chronic myocarditis and eventual heart failure.

Cerebrospinal Fever.—The importance of the anti-endotoxin content of antimeningococcus serum. GORDON (*Med. Research Council*, London, 1920, 93-109, Special Report Series, No. 50), in the course of his studies, found that an important factor in the pathogenicity of the meningococcus consists of a powerful toxic agent closely bound up with the bacterial protein. This endotoxin is liberated either by an external lysin or by the autolytic enzyme contained within the coccus itself. That the efficiency of an antimeningococcus serum is modified greatly by the quantity of anti-endotoxin it contains, is illustrated by the results obtained in the treatment of a series of cases in the London district. Here the mortality was 18.5 per cent. as contrasted with a mortality of 48 per cent. elsewhere. Investigation of the serum used in this district revealed the fact that its anti-endotoxin titer was high, whereas the sera used elsewhere possessed little or none as revealed by protection experiments. Later it became necessary in this same district to introduce a different lot of sera. The mortality immediately rose to approximately 50 per cent. From his studies Gordon concludes that anti-endotoxin is the most important individual antibody identified so far in antimeningococcus serum. He feels that the conception that cerebrospinal fever is a disease in which one of the essential features is the struggle between the endotoxin of the infecting agent and the ability of the patient to form anti-endotoxin brings this disease into line with infections in which serotherapy has achieved some of its greatest successes. At the time of this report the anti-endotoxin content of type i (Gordon) antimeningococcus serum was much higher than that of the type ii (Gordon) antiserum and the therapeutic results correspondingly better. Further work on anti-endotoxin serum for type ii infections is being carried out.

Diffuse Adenomatosis of the Thyroid Gland.—GOETSCH (*Endocrinology*, Los Angeles, 1920, No. 3, iv, serial No. 15, 389-402) reports the study of "borderline cases" in which the familiar syndrome of hyperthyroidism is present (asthenia, loss of weight, nervousness, labile pulsé, mild tachycardia, perspiration and tremor, occasionally depressions, often hyperpyrexia) but in which physical examination reveals no gross thyroid gland changes and no eye signs. The diagnosis in these cases lies between mild hyperthyroidism, incipient tuberculosis, various forms of psychoneuroses and perhaps certain chronic infections. In a series of 15 such cases in which the usual medical treatment had failed and which gave a positive epinephrin hypersensitiveness test the author advised operation—usually consisting of a bilateral partial resection of the thyroid gland. The author reviews briefly the accepted pathological change occurring in the gland which are associated with hyperthyroid symptoms: (1) Slight or moderate hypertrophy and hyperplasia of the alveolar epithelium surrounding the colloid, giving

rise to a mild hyperthyroidism such as occurs in association with the hyperplastic gland of puberty, pregnancy, menstruation, etc.; (2) more advanced alveolar parenchymal hypertrophy and hyperplasia, as in exophthalmic goiter; (3) discrete thyroid adenomata arising probably from individual groups of the interstitial epithelial cells (Wölfler) which occur in the interstices between the normal acini. To this classification of pathological thyroid changes associated with hyperthyroidism Goetsch adds a fourth which he calls "Diffuse Adenomatosis," and which is characterized by a general overgrowth of the interstitial cells (Wölfler) and hyperplasia of the acinar epithelium, as contrasted with the circumscribed overgrowth of the former which results in discreet adenomata. He reports 15 cases, mostly young adults, presenting a syndrome characteristic of possibly hyperthyroidism, incipient tuberculosis, neuro-circulatory asthenia and allied conditions. Eye signs and positive clinical findings in the thyroid gland were absent. They failed to respond to medical and hygienic treatment. Many failed to show increased basal metabolism. All gave positive reactions to the epinephrin test. Ten of the fifteen cases had had sanatorium treatment for tuberculosis; one was a case of paroxysmal tachycardia; one a case of weakness, nervousness and tremor of unknown origin; three complained primarily of nervousness and weakness. In each case an extensive bilateral partial lobectomy was performed, about three-fourths of the gland substance being removed. The glands from these cases showed fairly uniformly the changes which lead the author to introduce the term "Diffuse Thyroid Adenomatosis." The patients so treated showed from a moderate to a very remarkable improvement.

Metabolism in Tuberculosis.—McCANN and BARR (*Arch. Int. Med.*, 1920, xxvi, 662) give a detailed report of clinical calorimetric determinations on 15 cases of pulmonary tuberculosis, which they summarize as follows: "(1) The basal metabolism of tuberculous patients may be normal or very slightly above that of normal men of the same size. Thus, in 10 cases, the variation from average normal was from minus 3 to plus 15 per cent. (2) Further increases in metabolism occur with a rise of body temperature. These increases are not large. Thus 1 case was given in which the temperature rose 1° C. during two hours without a chill. The heat production of the second hour was only two calories greater than that of the first hour. With a rectal temperature of 104° F., the metabolism may be 30 per cent. above the average normal. (3) The basal heat production in tuberculosis may be less than the normal for the same patient when in health; in other words, the loss in weight may be accompanied by a reduction in metabolism which more than compensates for the tendency to increase caused by the disease. (4) Limited data regarding the nitrogen excretion show that, while a toxic destruction of protein does exist in tuberculosis, it is not large. The urinary nitrogen may be reduced to from 5 to 6 gm. per diem, though nitrogen balance may be attained only at a higher level (about 10 gm. a day). (5) The specific dynamic rise in metabolism produced in 2 cases by the ingestion of a protein meal corresponded closely with that produced by the same meal in three normal men." **Conclusions.** In view of the fact that the food requirements of tuberculous patients are not large, either as regards total energy value or

nitrogen content, forced feeding is unnecessary and is probably harmful in the active stages of pulmonary disease. Since protein increases the respiratory exchange in the tuberculous as in normals it may be well to limit the protein intake during periods of activity (of the disease) in order to put the lungs at rest.

SURGERY

UNDER THE CHARGE OF

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The Treatment of Chronic Empyema.—TUFFIER (*Annals of Surgery*, 1920, lxxii, 3, 266) gives us his conclusions, based on 91 cases of empyema which he operated on from August, 1914 to December, 1919. Exploratory puncture to determine the bacteriological nature of the effusion is of first importance. Pneumococcic pleurisies are mild and often cured by simple aspiration, while streptococcic pleurisies are grave and most often require thoracotomy. If repeated punctures leave a residuum as shown by radioscopy, thoracotomy is done in the postaxillary line. Evacuations of the effusions and disinfection of the pleura follow. Some cases can be closed immediately. Large cavities are dakinized. All of Tuffier's cases have been seen from six months to three years after operation. Thoracic deformity was slight. Chronic pleurisies are exceptional when acute effusions are well treated. Costal resection in the treatment of chronic empyema should be reduced to a minimum. Closure of the surgical incision and pleural decortication should be preceded by disinfection of the cavity.

Roentgenographic Appearance, Diagnosis and Pathology of Some Obscure Cases of Bone Lesions.—LOVETT and WOLBACH (*Surgery, Gynecology and Obstetrics*, 1920, xxxi, 2, 111) very carefully report with pathological findings 25 cases with obscure bone lesions. The cases presented are those in which there was, in the minds of the writers, doubt as to the correct diagnosis from the x-ray and other data available before operation. Considering the behavior of bone in general, as studied by the x-ray, it seems to be a structure of very limited reaction to pathological conditions. There seem to be only three reactions possible in bone: (1) atrophy or diminution in lime content; (2) destruction of bone tissue, local or general; (3) a formative process, characterized by the formation of new bone, or a condensation of existing bone around a focus of disease. The errors in diagnosis in the experience of the writers has been in mistaking tuberculosis for other things. The other troublesome confusion was between osteomyelitis and syphilis. The serious problem of differential diagnosis occurs most often in cases

in which focal lesions are present, in which the phenomena of formative and destructive activity have become so mixed that without pathological examination, in many of them diagnosis is impossible. The advantage of such a diagnosis made during operation is evident to the surgeon because it guides him in the treatment of the bone cavity. The diagnosis of infectious lesions of the bones would be simple if each infectious agent produced the same reaction. The pyogenic bacteria alone may be counted on to conform to this type. Syphilis affects the bone in two ways and results either in destruction of the bone or the new formation of bone. In tuberculosis of bone there may occur: (1) exudate, fibrinous or puriform, (2) discrete proliferative lesions, (3) a diffuse proliferative reaction, essentially tuberculous granulation tissue. Tuberculosis may simulate any other infectious process in location and character of the lesion. Diagnosis from x-ray studies alone is occasionally impossible.

The Treatment of Chronic Empyema.—HEDBLOOM (*Annals of Surgery*, 1920, lxxii, 3, 288) says chronic empyema has been recognized and treated during twenty-six centuries, but it is only sixty years since the first rib resection for drainage was done. The successive stages in the progress of treatment since that time are as follows: Increasingly radical treatment, designed to obliterate the cavity by the collapse of the chest wall, involving successively more extensive operations, and culminating finally in a complete radical resection. A conservative trend manifested primarily in the modifications of the complete resection, but more in the attempt to preserve the chest wall and to restore the lung to its structural and functional relationships as first advocated by Delorme. The adaptation of the Carrel-Dakin hypochlorite solution technic to the treatment of chronic empyema cavities. Chronic empyema is a disease which is not incompatible with life nor with a fair degree of health and usefulness. The principles of treatment should, therefore, be first, the preservation of life, and second, as far as possible, the conservation of function. Shortening convalescence, while very desirable, should always be a subsidiary consideration. The choice of treatment must be made with cognizance of the variable etiology and pathology of the process, and the general condition of the patient. A major procedure is indicated only if non-operative or less extensive surgical treatment reasonably may be considered less effective. In case of sinuses and small cavities, adequate drainage is usually sufficient to effect a cure with or without short preliminary hypochlorite solution treatment. It is at least open to question whether a radical operation is indicated in these cases for the sole purpose of shortening convalescence at the risk of an appreciably increased mortality. Dakin's hypochlorite solution treatment is the method of choice in the treatment of the ordinary type of chronic empyema cavity of any size, for the following reasons: The general condition of the patient is, as a rule, improved to a remarkable degree. The cavity may be obliterated or greatly reduced in capacity by the liberation and expansion of the lung (resulting from the treatment). If the lung expands in part the extent of a later operation will be proportionately reduced. If the lung entirely fails to expand, the cavity will have become relatively sterile in preparation for operation, thereby lowering postoperative morbidity and

mortality. Pulmonary decortication will be materially facilitated in some cases, owing to the softening action of the solution on the visceral pleura. A pulmonary decortication through a rib-spreading exposure after preliminary hypochlorite solution irrigation is the most conservative treatment for cavities that are not obliterated by drainage or Dakin's solution treatment alone. If such an operation is successful, the lung is restored to its normal structural and functional relationship, thereby obliterating the cavity. If the operation is only partly successful, the magnitude of a secondary destructive operation is proportionately decreased. Since it is impossible to judge with certainty before operation of the relative expansibility of the lung in every recent non-tuberculous case, a decortication should be done rather than a destructive operation, thereby giving the patient the benefit of the doubt. If the lung does not expand, or if a considerable cavity persists following decortication, a plastic operation is indicated. If the cavity is of considerable extent or the patient debilitated, a two- or three-stage plastic operation is to be recommended. The recognition of tuberculous empyema is often difficult. A history of a primary pleurisy with effusion seems more often to signify a tuberculous condition than does a pulmonary lesion, unless the latter is active and extensive. A tuberculous empyema may be present in the absence of clinical or x-ray evidence of pulmonary involvement. The typical microscopic picture in the sectioned pleura or the demonstration of the bacilli in the exudate may constitute the only evidence in such cases. A tuberculous empyema not secondarily infected should not be drained, and should be aspirated only for a considerable accumulation of fluid. For a tuberculous empyema secondarily infected, either by operation or spontaneously, drainage is necessary. In the absence of bronchial fistulas and of bleeding, secondarily infected tuberculous empyema may be markedly benefited by antiseptic solution treatment. The amount of fibrosis or other pathologic change in the lung in such cases determines the degree of expansion of the lung, whether following antiseptic solution treatment or decortication. If the lung fails to expand in whole or in large part, a several-stage operation designed to collapse the chest wall is indicated. Tuberculous patients are relatively poor operative risks. Adequate drainage is the first indication in cases of empyema cavities which are draining through large bronchial fistulas. The fistulas may be obliterated spontaneously following such treatment. Operative closure of bronchial fistulas that persist is necessary to complete healing. It may be accomplished by decortication of the involved portion of the lung with cautery, suture, or skin plastic to cover the opening of the fistula. Occasionally healing results from simple granulation of surrounding tissue after destruction of the epithelial lining of the bronchial stoma. Closing the bronchus that is draining pus from within the lung may result in a secondary lung abscess. A large bronchial fistula is a contra-indication to Dakin's solution treatment. Sinuses of variable duration are common following more or less complete obliteration of empyema cavities; a large proportion eventually are obliterated without radical treatment; for those which persist, plastic operation is indicated. Operative mortality in chronic empyema has been due largely to shock and infection. Reduction of the extent of operation and preliminary sterilization will materially lower this mortality.

PEDIATRICS

UNDER THE CHARGE OF

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OF PHILADELPHIA.

An Unusual Case of Cretinism.—KERLEY (*Arch. Ped.*, August, 1919) reports a case of a girl, aged eight and a half years, who weighed forty and a half pounds. She was thirty-seven and a half inches tall. She was a full term baby and weighed four and a half pounds at birth. She was breast fed for seven months and then bottle fed. Her growth was slow and she appeared backward in her development. Dentition began fifteen months, and she did not walk until her third year. Her appetite was always poor and there was habitual constipation. She was dull and inactive and took but little interest in her surroundings. On physical examination the heart, lungs, kidneys and blood were found to be negative. The abdomen was large and protuberant, and there was an umbilical hernia. The hair was dry and coarse and the nose flat and the lips thick, the skin dry and harsh and cool to the touch, the teeth poorly formed and decayed. The second set had not appeared. She could say only a very few words, had no interest in play nor in other children. She showed all of the classical signs of cretinism and was given a suitable diet and placed on one grain of thyroid extract twice a day. This was later reduced to a half grain. In a year and thirteen days she gained eight and three-quarter pounds in weight and grew six and five-eighth inches. Her mental improvement was remarkable and kept pace with the change for the better in physical appearance. The change in the character of the hair was most noticeable and the large umbilical hernia disappeared.

Some Remarks on Cranial Sinus Thrombosis in Children.—OPPENHEIMER (*Arch. Ped.*, January, 1920) reminds us there are two recognized forms of thrombosis—primary or marasmic; and secondary or infective or inflammatory. The latter is the more frequent type. The primary type usually is located in the longitudinal sinus, rarely in the lateral and still less frequently in the cavernous. It occurs during the first two years of life and more especially during the first six months. The diagnosis of primary sinus thrombosis in children is difficult and is seldom made during life. Secondary or infective sinus thrombosis is much more frequent than the primary form, and follows extension of inflammation of parts contiguous to the sinus wall. It occurs almost as frequently in children as in adults. It generally affects one of the dual sinuses. In its later stages, it is often associated with meningitis, and not rarely with small cerebral or cerebellar abscesses. The most frequent causes are the suppurative middle ear lesions. Males are affected more frequently than females, and the right lateral sinus is more frequently involved than the left. This is probably because the right is usually larger and closer to the mastoid cavity than the left. The symptoms are fairly constant, although in children they may be

masked by the presence of some underlying acute infectious condition. The temperature may be high. Chills are absent as a rule. The hands and feet may be often found to be cold. An important point is the taking of a two-hour temperature in order to note accurately the varying oscillations. Typical cases occasionally present themselves where the temperature remains steadily high without much remission. In older children there may be headache, pains in the occipital region, and tenderness on palpation along the jugular vein. A diagnostic sign of importance is the unilateral enlargement of the lymph nodes at the junction of the facial vein with the internal jugular. The cord-like feel along the border of the sternocleidomastoid is quite typical. There is often nasal hemorrhage. Drowsiness is frequent. Dysphagia is an important symptom. The treatment is entirely surgical.

Fluid Injections in Dehydrated Infants.—McLEAN and LANG (*Am. Jour. Dis. Children*, May, 1920) treated 76 infants showing signs of dehydration by giving fluid injections. These 76 children received 269 injections of fluid. Of these 155 were hypodermoclyses, 92 were intraperitoneal injections and 22 were sinus injections. The mortality was 56.5 per cent. The amount of clyses varied between 90 and 150 c.c., depending on the size and the condition of the child. In a few cases $\frac{1}{1000}$ to $\frac{1}{500}$ grain of atropin was used in the solution. On one occasion 120 c.c. of a 6 per cent. dextrose solution was used. The intraperitoneal injection fluids were of various formulæ, varying in amount from 150 to 240 c.c. Their records show worse results in infants receiving more than three injections than in those receiving less than three injections. In spite of this it was found that repeated injections usually do no harm. There was no relation between the weight of the infant and the mortality rate. The mortality was considerably higher in infants who showed a weight loss twenty-four hours after injection than in those who maintained their weight or gained. There was no marked difference in the death-rate of different age groups. A change of ten in the pulse-rate, of five in the respiration and of 1° of temperature are definite signs of reaction. The pulse was more frequently affected after sinus and intraperitoneal injections than after hypodermoclyses. The respiratory rate was more frequently affected in peritoneal injections than after sinus injections or hypodermoclyses. The temperature was more frequently affected after sinus injections. Weight gains were more frequently noted after intraperitoneal injections. It was also noted that the shorter the interval between the onset of symptoms and the beginning of treatment, the greater was the response.

The Value of Luetin in an Out-patient Department.—MEYERS (*Arch. Ped.*, April, 1920) tested 168 cases, of which 61 per cent. were males and 39 per cent. were females. The ages varied from eighteen years to seven weeks. The total number of positive reactions was 65.4 per cent. In practically every case that gave a positive reaction with the luetin test there was something in the history or physical findings indicative of syphilis. The family history suggested lues in 35 per cent. of the cases, while 30 per cent. was diagnosed from the clinical findings. The various reactions to luetin may be grouped under five distinct heads: papular, vesiculopustular, delayed or torpid, urticarial and hemorrhagic. The majority

were papular. After forty-eight hours there appeared at the site of injection a definitely indurated papule, 5 to 12 mm. in diameter, usually surrounded by a zone of redness of varying size. Over one-third were of the pustular type. In this type an indurated papule appeared in two or three days. It soon became vesicular, and after central softening this became a pustule, which ruptured and formed a scab. Several cases gave the delayed or torpid reaction. The primary papule soon disappeared and simulated a negative reaction. In ten to twelve days it reappeared and progressed to either a definitely indurated papule or a pustule, after which it followed the progress of the particular type. There were 3 cases of urticarial type. In about nine days after injection the lesion took on a distinct urticarial form about 8 mm. in diameter. In a few days it changed to a papule. There were only 2 cases of the hemorrhagic type. Instead of the lesion filling with pus it contained a hemorrhagic exudate. The test is a simple matter if the injection is made intracutaneously, and 65 per cent. of congenital luetics will react positively to the test. There are no constitutional reactions.

The Diagnosis and Treatment of Congenital Pyloric Stenosis.—HARDT (*Penna. State Med. Jour.*, May, 1920) says that this condition undoubtedly exists much more frequently than is diagnosed. The first symptom is vomiting, which frequently begins as regurgitation and gradually becomes worse until it become distinctly projectile in character. It occurs after each feeding or after several retained feedings. The character of the vomitus is not distinctive. The vomiting is the most alarming symptom. There is a peristaltic wave which appears after food is taken and radiates from the cardia to the pylorus. A tumor may be felt to the right and above the level of the umbilicus. There are scanty stools and urine and progressive loss of weight. Fluoroscopic examination is of great value in making the diagnosis, and it is further of value in determining whether or not the case is one for surgical treatment. The fluoroscopic technic consists of giving a small amount of bismuth in mothers' milk with the child in the horizontal position. While nursing from the bottle the mixture is watched as it passes through the esophagus into the stomach. The baby is rotated toward the right side, and as the bismuth gravitates toward the pyloric end of the stomach, peristaltic waves commence to be visible in the pyloric antrum and the pylorus. A small amount of bismuth is forced through, and as the pylorus closes tightly, peristaltic contractions can be seen which are independent of the rest of the stomach. The examination is repeated at the end of two hours and again at the end of four hours. If at the end of this time one-half of the bismuth remains in the stomach the case is considered a surgical one. The chief condition simulating this and which must be differentiated in diagnosis is pylorospasm. The most significant point in pylorospasm is that the vomiting and the peristalsis are much less marked, and it is usually observed in much older children. There is always absence of tumor in pylorospasm.

Intussusception in Infants.—EPSTEIN (*Ohio Med. Jour.*, June, 1920) reports 5 cases; 4 of these occurred in the summer, which fact together with the acute onset suggested gastro-intestinal inflammatory disease rather than intussusception. The alarming symptom for which medical

advice was sought was the hemorrhage from the rectum. The differential diagnosis from a follicular enteritis, the only form of gastroenteritis in which blood is present in the stools, is made by the presence of shock, a normal or subnormal temperature, absence of stools, a palpable tumor and a mass on rectal examination in intussusception. Rectal examination should be made in every case, with a history of blood in the stools. Another very important examination, that of the napkin, to ascertain whether there is a stool present with the hemorrhage or whether there is hemorrhage without a stool. The latter is indicative of intussusception.

The Influence of Epidemic Poliomyelitis upon the Susceptibility to and the Symptomatology of Other Contagious Diseases.—REGAN (*Arch. Ped.*, May, 1920) says that the occurrence of mixed infection constitutes a possible source of danger in the hospital treatment of all contagious diseases. This was considered particularly important as large numbers of children were admitted to the hospitals during the epidemic of 1916, at the ages of the greatest susceptibility to contagious diseases. Many gave no history of a previous illness. This was during a period of the year when contagious diseases were prevalent. Rashes of scarlatiniform type, with heavily coated tongue, congested throat and occasional minute spots on the buccal mucosa, which occur as part of the symptomatology of poliomyelitis, caused some confusion at first and many were isolated as possible cases of measles or of scarlet fever. The subsequent course of the cases showed that these phenomena were to be attributed to poliomyelitis. As the epidemic progressed the small incidence of mixed infection was noted. Regan observed in the Kingston Avenue Hospital only 15 cases developing a mixed infection, or 0.83 per cent., and if 9 cases of pertussis were excluded, only 0.33 per cent. These 15 cases were 9 of pertussis, 3 of diphtheria, 1 of measles, 1 of scarlet fever and 1 of varicella. No other children in the wards developed infections from contact with these in spite of the fact that the wards were filled with children, the majority of whom were unprotected by previous attacks. Not only was mixed infections of poliomyelitis with other contagious diseases slight, but the number of patients admitted with double infections of this and other contagious malady was also small. There were only 17 cases, or 0.94 per cent. Thus out of 1798 patients only 32 had on admission or developed subsequently another disease. The incidence percentage was 1.72. There were 22 with pertussis, and if these were deducted the incidence percentage would be only 0.59 per cent. These facts indicate that children with poliomyelitis are not as susceptible to develop other contagious diseases as are normal children, with the possible exception of pertussis. Regan offers the following working theory: Upon infection with the virus of poliomyelitis, certain changes occur in the tissues of the infected individuals, due possibly to the products of growth of the organism of poliomyelitis, which render them unsuitable for the development of the causative agents of other acute infectious diseases. In other words a condition of antagonism exists. It may be that the causative factor of poliomyelitis is so thoroughly distributed and so numerous in the nose, throat and upper respiratory tract that the infectious agents of the other acute infectious diseases find it difficult to find an atrium

in which they can develop sufficiently to invade the body. The only germ that seems to have a symbiotic relation with that of poliomyelitis is the bacillus of whooping-cough. The influence of poliomyelitis on the symptomatology of scarlet fever, diphtheria, varicella, measles and parotitis seems to be negligible, with the one exception that the symptoms of the associated disease seem more mild than is usual. The mortality rate of the mixed infections was very low, being only 3 per cent. as compared to 23.79 per cent. in the uncomplicated cases.

Biological Study of the Hemolytic Streptococcus from the Throats of Patients Suffering with Scarlet Fever.—BLISS (*Bull. Johns Hopkins Hosp.*, May, 1920) reports that in a study of 25 strains of Streptococcus hemolyticus, isolated from the throats of patients with scarlet fever, 20 strains, or 80 per cent., were agglutinated by four different antistreptococcic sera made with streptococci obtained from scarlet fever cases. None of these strains were agglutinated by five antistreptococcic sera of non-scarlatinal origin. Only three of seventeen strains of non-scarlatinal origin were agglutinated by these three sera of scarlatinal origin, and they may have been either atypical scarlatinas or scarlatinal contacts. There were certain differences in structural characteristics, particularly in the fermentation of carbohydrates. From this study it would appear that a great majority of strains of Streptococcus hemolyticus isolated from the throats of scarlet fever patients belong to a specific biologic type as determined by the reaction of agglutination. It is possible that the heterogenous strains found may be accidental dwellers in the throat and that a more careful selection of the colonies may reveal a still higher proportion of unit type organism.

The Effect of Intravenous Injections of Calcium in Tetany, and the Influence of Cod-liver Oil and Phosphorus in the Retention of Calcium in the Blood.—BROWN, McLACHLAN and SIMPSON (*Am. Jour. Dis. Children*, June, 1920) report observations on 14 cases of frank tetany, all of which showed varying degrees of rickets. They studied the blood calcium of 18 infants under one year of age. Then they observed the effect of intravenous injections of calcium acetate on blood calcium and on the symptoms of the cases of tetany and also the effect of cod-liver oil and phosphorus in the blood calcium and the clinical result. Constitutional reactions were produced following intravenous injections of calcium lactate in 1.25 gm. doses. The degree of reaction varied from the slight drowsiness to almost complete collapse, accompanied by dyspnea. The signs of reaction disappeared usually between one and seven hours; the more severe the reaction the more longer it took the patient to recover. Intravenous injections of calcium lactate in 1.25 gm. doses produces a temporary absence of both electric and mechanic signs of tetany, usually lasting from seven to ten hours. Calcium lactate injected intravenously apparently exerts no beneficial therapeutic effect, unless supplemented by the administration of cod-liver oil and phosphorus, and by this method the reduction of the tetanoid symptoms is a little more rapid than by the use of cod-liver oil and phosphorus alone. Cod-liver oil and phosphorus produces an increase in the blood calcium with a corresponding reduction in the mechanic and electric signs within a period of from ten to seventeen days.

OBSTETRICS

UNDER THE CHARGE OF

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The Diagnosis of Early Ectopic Pregnancy.—HEANEY (*Am. Jour. Obst.*, July, 1919) contributes a paper in which he analyzes the signs and symptoms of early ectopic pregnancy. He draws attention to the widespread opinion concerning appendicitis, and states that the medical profession is not equally alert regarding ectopic pregnancy. The family doctor is, as a rule, unfamiliar with the symptoms, so that when cases come to the specialist they have frequently been neglected. This is a condition which certainly deserves remedying. The education of the public is necessary, and students should be given a different conception of diagnosis and symptoms in these cases from that which is usually given in text-books. More attention should be given to the early unruptured cases. Stress has been laid for some time on cases that have ruptured and in which hemorrhage is present, and the student gets the idea that such cases constitute a majority of those that he will see. Very often ectopic pregnancy is not thought of unless the condition of the woman is serious. Most articles in books describe the pain as stabbing, tearing or lancinating. When a tube actually ruptures extreme pain is the rule. Before this, however, patients usually have more or less discomfort, backache or cramps, or an indefinite time before rupture oftentimes attacks of pain which are thought to be gas in the intestine have occurred at an indefinite period before operation. These cramps are intermittent and appear and reappear usually a few days before the case terminates in rupture. If in the subject of ectopic pregnancy the emphasis is to be laid on the severity of the pains it is like dwelling on the emaciation of a patient in cancer of the uterus. Evidently in such cases delay may be fatal. In the experience of the writer one patient who had ectopic pregnancy had not the slightest pain or discomfort. The patient's only complaint has been of intermittent bleeding of a month's duration. When the patient has gone to her regular period and then complained of cramps in the side of the pelvis or of gas pains it should be looked upon as possibly an ectopic pregnancy. Again, too much stress in taking histories is laid upon the existence of amenorrhea. The first suspicion of pregnancy is in the passing of the menstrual period and most of the cases coming to clinics with ectopic pregnancy, if a careful history is taken and the patient is questioned closely the fact that she has been irregular in menstruation will be elicited. The ordinary history is deficient in this as it usually states only that the patient is menstruating or has just menstruated. The obstetrician familiar with the inaccuracy of statements made by patients can usually by taking a good history and questioning the woman discover the real condition. Furthermore, on close questioning it will be found that the belated menstrual period was less in quantity and shorter in duration than normal. It is exceptional in ectopic

pregnancy to have profuse bleeding for a long time, but intermittent bleeding over a considerable period should arouse suspicion. The discharge may be only a bloody liquid discharge, with or without clots. As irregular bleeding is unusual the patient is liable to forget that she went over her regular period. If the patient was pregnant she usually ascribes the bloody discharge to the fact that in her own mind she fears that she is about to have an abortion. Every patient who has suspicious symptoms of threatened, imminent or incomplete abortion should be examined, with the possibility in mind that an ectopic pregnancy may be present. A diagnostic point of some importance is the fact that the patient will often refer cramps to the side of the pelvis rather than over the uterus. Students should be taught that this irregular bleeding is more typical of ectopic pregnancy than is the amenorrhea. Undue emphasis has also been placed upon the passage of a cast of the uterus or similar portions of decidua. It is difficult to obtain from the patient accurate statements as to what has actually been discharged from the uterus. While shreds of decidua may have been expelled they are usually passed with blood clots, so that the patient knows nothing about the fact that they have been discharged. It is also commonly taught that scrapings by the curette and pieces of membrane when examined microscopically give ground for making an exact diagnosis. It is often stated that if a uterine pregnancy is present, villi of the chorion will be found; but if the pregnancy is extra-uterine, decidual cells without villi are seen under the microscope. The absence, however, of chorionic villi in the discharges does not prove that a uterine pregnancy has not happened. There is no certainty in the examination of any pieces of expelled tissue. While the presence of chorionic villi proves that uterine pregnancy exists the absence of this villi does not prove, unless the complete decidual lining has been examined and a careful search reveals that no villi can be found. There is no certainty in examining pieces of expelled tissue only. After it has embedded itself in the decidua several weeks are required to bring the chorion in apposition to the decidua in all parts of the uterus. Before this occurs pieces of decidua may be expelled in uterine pregnancy, and should this decidua be festooned over the site of implantation then microscopic examination will not show villi of the chorion. While the presence of villi of the chorion is proved by intra-uterine pregnancy the absence of this phenomenon does not rule out uterine pregnancy. If a suspicious case be curetted and no decidua found this does not necessarily completely rule out pregnancy, for the uterus may have expelled its contents and the curette failed to obtain material for examination. This is especially true if the embryo is dead. In some cases of membranous dysmenorrhea without pregnancy decidual cells are found. Very few ectopic pregnancies pass any membranes as such, and in general it may be said that if the patient can give a clear history of having passed organized tissue the more likely it is that the case is one of uterine rather than ectopic pregnancy. One fallacy in current teaching is that the uterus enlarges in ectopic pregnancy. If this were to be true the ectopic pregnancy under these conditions, should the pregnancy go to near term, the uterus would be about as large as an ordinary pregnancy at the fourth month. The closer the ectopic sac is to the uterus the more rapidly does the uterus enlarge. As ectopic pregnancies are very

commonly interrupted early it is seen that enlargement of the uterus may in many cases be absent. At operation there is usually some enlargement of the uterus in a considerable percentage of cases, but in a large number the uterus is not above average size and frequently is less than the average. This may arise from the fact that ectopic pregnancy is most liable to develop in cases in which the development of the generative tract has been deficient. If the uterus be not enlarged and smaller than usual, if the patient has colicky pains and intermittent bleeding, the diagnosis of ectopic pregnancy may be on the average safely made. Again, the fact that the patient denies nausea or symptoms associated with the breast is not evidence of ectopic pregnancy. Should, however, nausea and breast symptoms be present they point toward a normal gestation. The writer states that we are taught that ectopic gestation enlarges the appendages of the uterus and that this can be made out by bimanual examination. A cystic corpus luteum will produce a temporary swelling which on bimanual examination might be taken for an unruptured ectopic pregnancy. The smoother the course of pregnancy the less importance should be placed on swelling of the appendages. Because the obstetrician cannot palpate a supposed gestation sac in a case of shock and pain he should not, therefore, conclude an ectopic pregnancy is not present. Many cases of ectopic pregnancy rupture gradually, with very little disturbance. The symptoms usually described apply best to cases of extensive and sudden rupture, but these do not comprise by any means all of ectopic pregnancy. There is a tendency to wait until air hunger or dulness in the flanks is present to complete the diagnosis of ectopic pregnancy and a dangerous condition of the patient. Emphasis should be placed upon the fact that the severity of the symptoms depends upon the quantity of blood lost more than upon the circumstance of rupture of the tube. Only small vessels are sometimes torn and the tear may be incomplete when the patient will have sudden pain, not very severe, followed by nausea and weakness. If the bleeding ceases the patient may soon feel as well as usual. When a considerable quantity of blood is lost the patient is usually pale, sweating, sometimes vomiting, and has a feeling of intense weakness. Air hunger and abdominal distention applying only to extensive and sudden hemorrhage. While there may be only very decided hemorrhage in the case, close questioning will bring out the fact that there has been a number of attacks of indefinite pain with some discharge. In any woman of child-bearing age seized with abdominal pain of severity, followed by shock or syncope, even though brief, the case must be regarded as a possible one of ectopic pregnancy until it can be proved to be otherwise. A blood count may assist in diagnosis. When the hemorrhage has been moderate the blood findings are not sufficiently characteristic to warrant a diagnosis of internal hemorrhage. As a leukocytosis is present the obstetrician may believe he is dealing with appendicitis. It is the rule that in ectopic pregnancy the leukocyte count is but little disturbed when the pregnancy is unruptured. After rupture there occurs a rapid increase in leukocytosis, and this becomes pronounced the larger the quantity of blood lost. A leukocytosis with a normal or subnormal temperature in a person who has had severe abdominal pain, followed by nausea and perhaps vomiting, should lead to a diagnosis of probable ruptured ectopic pregnancy. Emphasis

should also be laid upon the value of the exploratory vaginal incision in doubtful cases. This may make a diagnosis plain and justify immediate operation. Cases are sometimes sent to hospital where the condition is suspected but cannot be proved. These patients are repeatedly kept for observation, as the obstetrician is afraid to let them return to their homes. With such patients under observation a positive diagnosis should be made, and here vaginal incision is especially valuable.

GYNECOLOGY

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Radium Treatment of Menorrhagia.—In the Mayo Clinic, according to STACY (*Amer. Jour. Roentgenology*, 1920, vii, 379), surgery is still the treatment of choice for young women who have definite fibroids causing menorrhagia, or for those who have a normal sized uterus but a history suggesting the presence of an intrauterine polyp or small submucous fibroid, and for those with a history suspicious of malignancy of the fundus of the uterus. They believe that the large fibroids are best treated by hysterectomy as a certain means of quickly removing the tumor, without the possibility of degenerative changes occurring later. It has been their policy to limit the use of radium to fibroids the size of a three and one-half to four months' pregnancy, unless there is a definite contra-indication to operation. A hysterectomy should be advised in the cases in which there is a history suggestive of malignancy, for a negative diagnostic curettement is not to be relied on in the definitely suspicious case, as the curette may miss the involved area. In the young woman who has a definite fibroid causing menorrhagia, an abdominal myomectomy is the preferable treatment. By this method the tumor is removed, the menorrhagia controlled and a uterus is preserved which is capable of carrying on the functions of menstruation and child-bearing. If a young woman has menorrhagia without a demonstrable tumor which cannot be controlled by medical treatment or by curettement, an abdominal hysterectomy may disclose a small submucous fibroid or polyp so situated that it could not be reached by the curette. In the series of 600 cases treated by radium, on which this report is based, 122 women were under thirty-five, while 19 were twenty-five or under. The average dose of radium given to these patients was 293 mg. hours. Menorrhagia was controlled by one treatment in 55 per cent. of the cases. In 25 cases the periods were reported normal in amount, in 11 irregular and scant and in 6 menstruation

ceased. They attempt to give the women under thirty-five enough radium to control the symptoms, but not enough to stop menstruation, and it is difficult to judge the amount necessary in each case. It is better to give a small dose, however, and if there is a recurrence of the profuse flow, repeat the dose in from three to six months than to give enough at the first treatment to stop menstruation. Patients over thirty-five are given larger initial doses, as it is not so important that menstruation shall continue, but they always try to give a dose to all patients under forty which will control rather than stop menstruation. They have seldom given more than 50 mg. for fourteen hours at one treatment, since they believe that it is better to repeat the treatment if necessary, as it is sometimes in cases of a fairly large tumor. In a series of 349 patients it was necessary to repeat the treatment in 64 and an operation was done later in 20. Only 4 of the 20 had been given a second radium treatment and two had operations elsewhere too soon after treatment to obtain the effect of the radium. Menstruation became regular and normal in 11 per cent.

Ovarian Therapy.—In the light of theoretic, experimental and anatomic knowledge combined with long-continued observations, our general estimate of the ovary as a gland of internal secretion has been briefly summarized by GRAVES (*New York Med. Jour.*, 1920, cxii, 697) as follows: For complete somatic growth and sexual development the normal secretion of the ovary is essential. To what extent the action of the secretion is direct and how far it serves as a balance to other more powerful secretory influences is a matter of speculation. During menstrual life, and especially during the years of adolescence, the proper functioning of the ovaries has a very important bearing on the physical and mental character of the individual. Disfunctions of the ovaries are usually attended with various neuroses. Some of these may be due to the direct disharmonious action of other endocrines, especially those that have an affinity for the autonomic nervous system. In the adult the ovarian secretion plays a somewhat minor role in the human economy, as is indicated by the comparatively slight physical changes that take place after ablation or the natural menopause. This has an important bearing on the question of removing the ovaries during hysterectomy. During adult life the most definite evidence of the existence of a true internal secretion from the ovaries is the occurrence of hot flushes and genital atrophy after ablation. These symptoms point to a balancing rather than a direct action of the ovarian secretion. From an organotherapeutic viewpoint the ovary must be regarded as primarily a homogeneous gland, the essential secreting structure being the interstitial cells. Variations in secretion of different parts of the gland are probably differences of degree rather than of kind. A selective action of the secretions from different parts of the gland is not yet proved, and if it exists is probably quantitative. The therapeutic value of ovarian preparations in Graves's experience may be stated somewhat as follows: All the ovarian preparations exert a specific influence on hot flushes. In this respect the residue is the most intensive, but the difference in the efficacy of the various preparations depends to some extent on the idiosyncrasy of the patient. In the treatment of menstrual irregularities ovarian extracts exhibit an

undoubted specific action but this action is inconstant. In temporary functional amenorrhea, delayed menses, dribbling before and after catamenia and small clotting, ovarian therapy is fairly reliable, and is at least the best asset that the gynecologist at present possesses for these symptoms. Theoretically for these affections the ovarian action may be enhanced by the addition of thyroid and pituitary extract, but of this Graves's personal clinical experience has not been entirely convincing. For the permanent amenorrheas, especially those associated with pluri-glandular disturbances, ovarian therapy has little or no effect on restoring the menstrual function, but is of undoubted value in improving the patient's general health. It is best in these cases to administer the ovarian treatment in considerable doses, separately from the other gland extracts. In certain types of dysmenorrhea ovarian feeding is efficacious, occasionally brilliantly so, but it is unreliable and often disappointing after giving early promise. In the severe types of dysmenorrhea it is of comparatively little help. For menorrhagia and metrorrhagia ovarian therapy is not indicated.

Ovarian Transplantation.—There can be few gynecologists who have never had the experience of being obliged to open the abdomen at a longer or shorter period after a previous operation for salpingitis, because an ovary that had been left had become bound down with adhesions and was cystic. Encountering a number of these cases in his practice, BELL (*Lancet*, 1920, exciv, 879) came to the conclusion that it is not worth while leaving an ovary in a badly infected area, when further conception is impossible owing to the frequency with which subsequent lesions occur. Some surgeons have solved this problem by frankly castrating the patient, but Bell has adopted the method of ovarian grafting. His first operation on the human subject was performed in 1912, but it was not until 1916 that he adopted the procedure as a routine practice in certain well-defined circumstances. The following points in regard to the technic of this procedure are important: All grafts in the human subject must be autoplasmic. After the ovaries have been removed the ovarian tissue from which the graft is to be cut should be dropped to the bottom of the pouch of Douglas, where it will be kept warm and moist until the end of the operation, when it is required for grafting. When possible, healthy ovarian tissue, which may include all the elements of the organ, should be used. This should be criss-crossed with a sharp knife into adherent fragments after the dense tunica albuginea has been removed, in order to favor rapid vascularization of the grafted tissue. The graft, provided there is no suppurative infection of the ovary, may be placed in the rectus muscle before the laparotomy wound is closed. He has also implanted the graft in the uterus or in what was left of this organ. It is most important that the graft should be placed in a vascular site, but should not be surrounded with blood. Too much care cannot be taken in placing the graft among the muscle fibers. If the ovaries be badly infected and more or less completely converted into the walls of abscess cavities, whatever tissue can be removed should be implanted in the internal oblique muscle alongside the drainage tube, which in such circumstances is passed through a stab wound well away from the central incision into the pelvis. He has never seen an infected graft slough; moreover, in

several such cases menstruation has subsequently occurred. In only a few cases is menstruation regular after ovarian grafting. It usually recurs at longer intervals than normal—that is to say, every six weeks or two months. Some patients menstruate a few times and then cease and minor symptoms of the menopause may appear. Bell's conclusions, based on a fair experience, lead him to advocate very strongly the practice of ovarian grafting in suitable cases. Nevertheless, he insists that this procedure be looked upon as a measure of necessity, which can never be weighed in the balance against the preservation of the natural connections of the normal ovary.

PATHOLOGY AND BACTERIOLOGY

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A Study of the Oxidase Reaction with A-Naphthol and Paraphenylenediamine Tumors.—The work reported by MENTEN (*Jour. Cancer Res.*, 1920, v, 321) consists in the application to tumor tissue of an oxidase technic previously studied in detail in various types of normal tissue. The reagent used was an aqueous solution of a-naphthol and paraphenylenediamine and when frozen sections of tumors were placed in this solution there developed within them a blue violet color whose intensity varied according to the type of tumor and the functional activity of its cells. While diverse types of neoplasms were studied the most striking results were obtained in fibrosarcomata where all gradations of color from a maximum in the degenerating areas to a faint reaction in the actively growing parts were met with. In the latter the color appeared only in the fine perinuclear granules which had a faint mauve appearance. The nucleus was free from any reaction. As the cell matured the reaction deepened to a violet in the perinuclear region and the chromatin was perceptible in the nucleus as faint mauve threads and knots. When through lack of adequate blood supply degenerative changes occurred in the cells the oxidase reaction became still further increased in the perinuclear granules and the nucleus and finally in the late stages of the degenerative process the whole cell protoplasm was converted into clumps of blue-black stained material. An attempt is made to interpret the phenomenon observed on a physicochemical basis. Since the development of the color is dependent upon the oxidation of the reagent and oxidation is due primarily to the acquisition of a positive electric charge it is postulated that any increase in the intensity of the color is due to the liberation of a positive charge within that tissue. That increased acidity occurs in degenerating tissues is a

well attested fact. The liberation of this positive charge within the cell is accompanied by conversion of potential into kinetic energy. In the actively growing parts where the oxidase reaction becomes progressively diminished, the reverse process occurs. It is assumed that it is those granules with high lability as manifested by wide variations in the oxidase reaction which most readily tend to become the primary site of metabolic changes of the nature of an anaplasia.

The Peroxide Reaction in Three Cases of Multiple Myeloma of the Bones with Remarks Concerning the Nosological Position of these Tumors.—Owing to the lack of definite knowledge concerning the origin of the cellular elements of multiple myeloma of the bones, a considerable confusion as to their proper classification has arisen. The various views which have been suggested as to the histogenesis of these rare tumors are fully discussed by MORSE (*Jour. Cancer. Res.*, 1920, v, 345) who has studied three cases, the autopsy findings of which are reported in detail. The gross appearance of these new growths is very characteristic. They arise in the bone marrow by multiple foci whose extension causes marked erosion of the bone. There is little or no tendency to callus formation or reparative processes. Metastases occurred in one of the cases reported by Morse. Microscopically the tumors are composed of cells irregularly oval in outline and contain an eccentrically placed nucleus. The nucleus is vesicular and shows a characteristic mural arrangement of the chromatin. The protoplasm is basophilic. Because of the close resemblance morphologically of these cells to the plasma cell and further because they react negatively to both Goodpasture's and Evan's oxidase technic, Morse concludes that they are not of myeloblastic origin and have no relationship to the leukemic group, but that "they spring from a series of cells whose specific function is bone absorption." It is suggested that they are related to the osteoblast and may be considered as heteroplastic osteoblasts.

The Biliary Factor in Liver Lesions.—ROUS and LARIMORE (*Jour. Exp. Med.*, 1920, xxxii, 249) attempted to arrive at a better understanding of the share of bile in the causation of hepatic lesions distinguished by a cirrhosis with evidence of stasis in the finer bile ducts and inflammation in their walls, by producing in rabbits obstruction to the bile flow at different levels. The authors confirmed the work of previous investigation in producing bile stained parenchymal necrosis after obstruction of the common duct, which was followed by a spreading stellate cirrhosis and connective-tissue proliferation throughout Glisson's capsule, resulting finally in a roughly hob-nailed organ. This rabbit lesion is mixed, involving injury throughout the biliary tract. By causing local obstruction at different duct levels, the authors attempted to produce cirrheses of uncomplicated types, resembling lesions in man. The bile duct and portal branch to the main liver mass of rabbits were ligated. There was found to result atrophy of the lobule and an evenly distributed monolobular cirrhosis. When the portal trunk of the main liver mass was ligated and seventeen to twenty-three days later the bile duct from this region was ligated, the main liver mass was found to have undergone atrophy. There was no icteric tinting of the parenchyma or dilatation of the bile passages. Evidently a very slight increase of

pressure within the ducts checked secretion into the normal channels. Yet, when the material for bile formation is provided in unusual quantity, by injecting hemolytic serum intravenously, a parenchyma deprived of portal blood can secrete bile into the ligated duct under considerable pressure. Intralobular stasis, and its corollary intralobular cirrhosis, can be brought about in the liver of rabbits by diverting the whole portal stream and ligating the efferent duct. When the duct from the main liver is also tied, the secretory activities of the lobe become strikingly evident, the lobules showing intense bile staining and intralobular cirrhosis developed rapidly without necrosis, as the increased portal flow provides a circulation to cells that otherwise would have been deprived of it. The authors conclude that the principles illustrated in their experiments may be applied to the biliary lesions of man, though the picture in man is varied by the fact that human bile is relatively non-irritant, that infection occurs more frequently in areas of stasis, and the liver parenchyma responds but slowly to deranged circulatory conditions. It is the belief of the authors that the diversity of the liver changes in man depend upon the duct levels at which the injurious agent is active, and that bile stasis may complicate any chronic liver derangement in which the bile passages are compromised.

A Rapid Method of Pneumococcus Typing.—Because of its value in prognosis and for specific serum therapy several methods for the determination of pneumococcus types have been devised. OLIVER (*Jour. Infect. Dis.*, 1920, xxvii, 310) employs a procedure based on the solubility of the pneumococcus in bile. The relative number of pneumococci is determined by a direct smear of the sputum stained by Gram's method. To one and one-half c.c. of sputum is added a sufficient quantity of normal salt solution to insure a homogeneous specimen which can be filtered or centrifugalized and the mixture is thoroughly stirred with a glass rod. From 3 to 5 drops of undiluted ox bile are then mixed with the diluted sputum, which is then heated to 45 to 48° for ten to twenty minutes in a water-bath. The fluid is then filtered or centrifugalized. Of the filtrate or centrifugate, 0.3 to 0.5 c.c. are pipetted into each of three small tubes. To the first tube is added one drop of undiluted type one pneumococcus antiserum, to the second, one drop of type two antiserum and to the third tube an equal quantity of type three antiserum. A positive precipitin test consist of a clouding which is enhanced by heating to 40° C. for ten to twenty minutes. If then placed in the ice-box for several hours the positive tube will show sedimentation. The method was used on 25 cases. In all of those where a positive precipitin test for one of the first three types of pneumococci was obtained, the results were identical with those obtained by the Avery method. In the 15 cases in which the rapid precipitin test was negative, the Avery method revealed a type four pneumococcus in 11 and streptococcus in 4. Of these 15 cases, intraperitoneal inoculation of mice with washed sputum was employed in 10, and each time the result was the same as in the Avery method. The author suggests the subsequent use of the mouse on those sputa in which the rapid precipitin test fails to reveal a type.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Masked Juvenile Tuberculosis.—COOKE and HEMPELMANN (*Am. Rev. Tuberc.*, November, 1920, iv, 660) believe that masked juvenile tuberculosis presents a sufficiently distinctive clinical type to deserve a prominent place in the category of tuberculous affections in childhood. They state that the characteristic clinical picture may be briefly sketched as follows: a history of frequent coughs and colds, with or without known exposure to tuberculosis, attacks of unexplained fever, often with afternoon elevations, anorexia, loss of weight and asthenia. On physical examination, there is found more or less malnutrition, occasionally anemia, and chest signs referable to enlarged tracheobronchial nodes. In certain instances there may be in addition phlyctenular disease or skin tuberculides. The Pirquet or intracutaneous tuberculin tests are positive, and, in those over four years of age, three-fourths of the children give a positive complement-fixation test for tuberculosis. The chest findings may be verified by the use of the roentgen ray which not infrequently reveals unsuspected lesions of varying size and age in the lung parenchyma as well. The diagnosis must of course rest not in any one of the points mentioned, but rather upon a review of all the findings; and there the authors wish to emphasize the value of the complement-fixation test in calling attention to this class of cases.

Saliva-borne Infections: Their Transmission through Eating Utensils.—CUMMING, SPRUIT and REUTER (*Mod. Med.*, July, 1920, No. 7, ii) conclude as follows from their investigations on saliva-borne infections: First and foremost in the control of the saliva-borne infections is a reduction in the transmission rate. This will diminish the large mass of carriers, who are far more important as sources of distribution for this group of infections than the actual cases in the hospital. Further attempts should be made to determine with accuracy the major and minor routes of transmission and the several links in the chain of these routes. The authors conclude from their studies that it appears eating utensils rank foremost as transmitting agents of the saliva-borne infections. These utensils either enter the mouth or touch the lips; they become contaminated with organisms of the oral cavity; they are still contaminated after they are hand washed, and the next user acquires this contamination. The use of utensils contaminated with organisms of one or more of the saliva-borne diseases does not necessarily mean infection, but this major avenue of transmission is so prolific and so

universal that a large number of saliva-borne infections occur and cause more deaths than all other groups combined. There is no avenue of indirect transmission more frequent than through insanitary eating utensils. We eat three times a day with utensils previously used by others; these utensils are not rendered aseptic; they actually enter the mouth—the normal portal of entry of the saliva-borne infections, and preventive measures must take them into account. The greatest hope for the control of this group of infections, especially tuberculosis and the fatal secondary pneumonias, lies in the universal practice of eating-utensil pasteurization by the use of boiling water. This applies alike to the home and the public eating place. In the home, eating utensils should be scalded before they are washed; in the public eating places they should be scalded in the process of mechanical washing. In public eating places this procedure of cleansing is not only economical, but its value as a public health measure in eliminating the primary center of saliva-borne disease distribution should be recognized.

Fatigue and Efficiency of Smokers in a Strenuous Mental Occupation.—BAUMBERGER and MARTIN (*Jour. Indust. Hyg.*, 1920, ii, 207) report the results of an investigation of the industrial efficiency of persons using tobacco in different amounts. Many studies have been made of the effects of tobacco on the human body, but probably no industrial output study of smokers and non-smokers has been reported hitherto. The authors state that if the data on which they base their conclusions are representative, two respects in which heavy smokers fail to maintain the level set by light smokers in a strenuous mental industrial occupation are established; namely, in a lessened ability to sustain output to the end of the working day, and in a diminished power to react by increased effort to an increase in the volume of business. They indicate, also, in favor of heavy smokers, a better output during the first hours, although this does not amount nearly to enough to compensate for the lowering of efficiency toward the close of the day. On the whole, they constitute an argument in favor of moderation in the use of tobacco on the part of industrial workers whose tasks fall in the category here under discussion. This conclusion is in line with the findings of various investigators of the records of college students and also football players: that extensive use of tobacco goes hand in hand with relatively low scholarship. It is probable, moreover, that no class of men is oftener advised by physicians to use moderation in consumption of tobacco than that made up of business executives, men who habitually do mental work under tension. All these facts are in line with the conclusion that strenuous mental work is likely to be affected adversely by heavy smoking.

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ORIGINAL ARTICLES.

THE IMPORTANCE OF RECOGNIZING AND TREATING
NEUROSYPHILIS IN THE EARLY PERIOD OF THE
INFECTION.

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A COMPREHENSIVE grasp of the syphilis problem cannot be obtained by the study of one phase only of the disease. A degenerated brain or a tract sclerosis studied by the neuropathologist visualizes the end-result of the treponema infection. It does not reveal the early beginnings of the disease nor indicate the therapeutic measures which might have prevented the terminal stage. The sudden onset of cerebral or spinal symptoms should not necessarily be interpreted as the result of an immediate invasion of the nervous system but rather as a tissue reaction of slowly progressive character. A close analogy is afforded by the study of the aortic changes in aneurysm as related to the early involvement of the adventitial vessels. The same arguments may be employed in the study of the visceral and other lesions in syphilis and conclusions deduced that degenerative changes are of slow progress and often require years before functional impairment is manifest. We must furthermore recognize the fact that the fundamental reactive phenomena are the same in the initial lesion which ushers in the infection and the vessel changes in paresis which end the luetic tragedy.

It seems needless to emphasize the importance of the study of syphilis as a general infection and the necessity of correlating the

observations of all medical workers who have to do with it. Various specialists observe the local lesions in the eye, throat, skin and other organs, and can often control them by short courses of treatment. These *manifestations* are the accidents or episodes of a general infection. The cure of visible lesions does not mean the cure of the underlying disease. It progresses in a modified manner in other tissues which are not seen and is then known as latent asymptomatic syphilis, an unfortunate expression which deceives the patient as well as his medical adviser. Syphilis of the nervous system should be restudied from both the clinical and serologic standpoint and the significance of the earlier infection emphasized in its bearing on the later degenerations. The highly specialized character of medical practice does not permit any one observer to see more than a few phases of the disease. Close and sympathetic coöperation between workers in many specialties can better advance our general knowledge. Institutions which contain individual groups, each willing to learn from the other, offer the best opportunities for mutual advance. In the past the dermatologist has emphasized chiefly the external evidences of the disease and has neglected in great measure the widely disseminated infection. Fortunately this criticism is no longer valid, as many observers are now engaged on the problem of the general disease in its relations to future changes in the nervous system and viscera.

The infectious agent in syphilis in its relation to the defensive forces of the body is analogous to other protozoan organisms. It may be modified, but is seldom controlled, by antibody or other immunity processes. Tissues may harbor the *treponemata* for an indefinite time with little or no evidence of their presence. It has been demonstrated time and again that the nervous system may be the habitat of the organisms, with little or no tissue reaction, until *a traumatism or some exciting factor stimulates their activity*, or until sufficient time has elapsed to permit centers or tracts to be compromised which give rise to objective signs or symptoms.

As a routine method of examination and control, spinal fluid examinations are made by few physicians in early syphilis. From this neglect many cases are overlooked because of their asymptomatic character. As time progresses these asymptomatic cases may develop vague mental or physical symptoms which are frequently wrongly interpreted by their physician until definite focal signs make their appearance. At this time neurosyphilis is said to exist, but little or no attempt is made to correlate the end-result of the infection with the indefinite signs and symptoms which have preceded. The failure of therapeutic methods to cure the terminal results of an infection leads to pessimistic views as to the utility in any stage and permits the diffusion of a large amount of false and misleading information.

Physiologic knowledge leading to the employment of exact

methods in diagnosing well-established focal lesions and tract degenerations has reached a high degree of perfection. It affords the physician much gratification to accurately determine the site of pathologic changes. The patient at this stage of his disease is an interesting study in brain or cord localization. The activity of a syphilitic process in the central nervous system is, however, indicated much earlier, more accurately and often only by the cytologic changes in the spinal fluid which should always supplement the physical examination. No matter what views we may hold as to the physiology or origin of the fluid the activity of syphilis of the central nervous system is usually reflected in the well-known phases of Nonne and the gold sol reaction long before mental or physical signs are present. Failure to utilize this important method of investigation in early syphilis leads inevitably to many unrecognized and slowly progressive types of neurosyphilis. Neglect of systematic eye-ground examinations in the active stage of the disease will likewise cause many cases of beginning optic neuritis to be overlooked.

Why should one await advanced degeneration in important organs and stand helpless in their presence when their early beginnings may be detected? The fate of a syphilitic individual as regards his future immunity to neurosyphilis rests largely on the result of a spinal fluid examination, either during his treatment or before his final discharge, and if infection is present, on its complete clinical and serologic cure. Both the patient and the physician are too often satisfied with a symptomatic cure and a disappearance of the obtrusive signs.

A prolonged study of early cases of neurosyphilis as regards the therapeutic response of the fluid changes to treatment has convinced me that on the one hand we have superficial types rapidly curable and on the other deeper ones which yield only to prolonged treatment. In their therapeutic response and fluid formula the latter are probably of the preparetic type which without treatment would eventually result in degenerative encephalitis.

By piecing together scattered observations supplemented by a certain amount of scientific imagination a mosaic can be constructed which conveys a picture of this far-reaching disease. The long experience, careful observations and keen clinical insight of Alfred Fournier, who saw all phases of syphilis, enabled him to interpret its relationship to tabes, paresis and other affections of the central nervous system which he designated "parasyphilis." Had he then been able to supplement his clinical observations with the modern discoveries of the *Treponema pallidum*, complement-fixation reaction and the cytobiology of the spinal fluid the necessity for devising the term "parasyphilis" would not have existed.

As the result of animal experimentation we can now follow the treponema from its first implantation and note the reactive phe-

nomena which attend its deposition in the tissues. Likewise clinical and pathologic studies in human syphilis afford good reasons and some direct observations which make it probable that foci are established in the various organs during the early florid stage of the disease. These foci may slowly cause tissue changes or the organs may harbor the treponema without reactions for an indefinite time. In numerous publications I have presented certain arguments based on observations and study of the general pathology of the disease which have convinced me that practically all types of neurosyphilis originate within the first year of the infection, and are then amenable to properly applied therapeutics. The results following the practical application of this working hypothesis have fully justified its adoption.

The experimental work of Nichols, Reasoner and others, supported by the clinical observations of many investigators as to the existence of familial types of neurosyphilis, afford strong arguments in favor of a strain of the treponema with neurotropic affinities or rapid invasive power. The absence of skin manifestations in a large percentage of cases of syphilis of the nervous system further distinguishes this strain from the usual one. Because of its greater invasive power or its attraction to nerve tissues it implicates these structures early in the infection in about 25 per cent. of all cases of syphilis. The number of cases revealed by fluid examination in the early period of the disease corresponds roughly with the total number of cases of late neurosyphilis. We are obliged, therefore, to conclude that either the cases of early syphilis of the nervous system are cured, and that another and later invasion occurs, or that the early infection persists in the majority of cases uninfluenced by the usual therapeutic procedures.

Our clinical and serologic study of syphilis during the past ten years has definitely shown us that in the great majority of cases syphilis of the nervous system is not cured by the use of specific remedies employed in the usual way. Many symptoms disappear, the blood Wassermann becomes negative and the patient enjoys for a time a feeling of false security, only later to awaken to a knowledge of his real condition. For instance the case of Dr. A., who acquired a digital chancre in March, 1913, while performing an abdominal operation. In April he presented a macular rash and complained of severe pain along the vertebral column, which rendered motion almost impossible. He received sixteen injections of arsphenamin and two courses of mercury. The Wassermann was repeatedly negative. In January, 1918, he had a fainting attack. The Wassermann at this time being reported 2+ he took seven more injections of arsphenamin and a course of mercurial injections. The reaction again became negative. Another fainting attack occurred in April, 1920. Pains in the shoulders and over the chest had also been present for several weeks. Neurologic

examination showed only the slightest difference in the deep reflexes on the two sides and the right pupil a trifle larger than the left and a little more active. His blood-pressure was 140/108. Lumbar puncture revealed 195 cells; globulin, 4+; Wassermann, 4+ to 0.1 c.c.; gold sol luetic curve. The blood was negative with cholesterinized antigen and 2+ with alcoholic antigen (ice-box fixation).

Another case is F., aged thirty years, who was treated intensively during the early secondary period of his infection, which occurred in May, 1912. At first he was given neoarsphenamin, 1.2 gms. every other day for three doses; then three more same dosage at six-day intervals, followed by three injections of 0.75 gms. at weekly intervals and five injections of arsphenamin of 0.4 gms. In addition he had thirty-two injections of mercury salicylate, grains $1\frac{1}{2}$ to grains $2\frac{1}{2}$. The Wassermann was persistently negative and remained so after a provocative injection three years after infection. Consent to a lumbar puncture was not obtained. Recently he returned for another blood test and complained of vague pains in his arms and legs. The blood with all methods was 4+. His deep reflexes were more active on the right than on the left side. There were no pupillary changes or other physical findings. Spinal fluid revealed: Cells, 55; globulin, 3+; Wassermann, 4+ with 0.6 c.c.; gold sol luetic curve.

Observations of a similar kind several years ago caused us to modify our criteria of cure and to insist on a spinal fluid examination before final pronouncement. If the spinal fluid is negative in all its phases after the other criteria of cure are complied with we can assure our patient, with a considerable degree of confidence, that he need have no fear of late neurosyphilis. In other words it is strongly probable the treponema invades the nervous system during the period of general dissemination or not at all.

One can readily see without a great tax on the imagination what enormous significance the general adoption of such examinations leading to proper diagnosis and treatment must have on the individual and what great economic importance it will have for society and the state. The question will doubtless be asked as to the reasons for the belief that infection of the nervous system does not occur later than in the early florid stage. We have not yet sufficient data to deny absolutely its possibility, but the arguments previously brought forward would seem to show that, as a usual method of infection of the central nervous system, in the light of our present knowledge of the cytobiology of the fluid it is extremely improbable.

In order to make scientific progress it is necessary, in the absence of exact knowledge, to adopt a plausible working theory based on known facts. If disproved by further observations it should be modified or discarded for one which more accurately accords with them. The theory in question is one which accords with many known facts. Properly employed therapeutic procedures controlled

by examinations of the spinal fluid cure practically all cases of early neurosyphilis. In none of the cases cured serologically and clinically have we seen later active recurrences. If subsequent experience confirms these results we may safely assume that it is possible to eradicate absolutely the most feared of all the results of the disease.

The alternative procedure to the method I have outlined is the one usually followed, *i. e.*, treatment with arsphenamin and mercury for one or two years. After a negative Wassermann in the blood has continued for a definite time the patient is told the cure is complete. He returns within a few years or sooner with pupillary changes, modifications in his deep reflexes and other indications of nervous system involvement. If he is fortunate enough to fall in the hands of a practitioner who realizes the significance of the signs in question, and believes in the revelations of spinal fluid examinations, he may yet be amenable to prolonged treatment. As a rule these cases are overlooked or a wrong interpretation is placed on their signs or symptoms. Their disease progresses to the terminal degenerative stage.

The old view that the organism of syphilis may disseminate and invade the central nervous system at any time has nothing to support it except vague clinical impressions. It could only be determined by spinal fluid examination showing absence of early infection and by similar examination in the late stages proving the existence of it. No such proof exists, while all the evidence supports the contrary view. We have everything to gain and nothing to lose by adopting the hypothesis in question. We have everything to lose and nothing to gain by adherence to the older view.

It will require many years before practitioners of medicine fully realize the relationship of early involvement of the nervous system to the later degenerative stages of paresis and tabes and the importance of controlling the final cure by systematic fluid examinations. It will require a longer time before these early infections are systematically and properly treated. Until our public clinics are provided with proper facilities for diagnosis and treatment such cases will go unrecognized and neurosyphilis will continue to cut short the lives of many otherwise useful citizens. The need of better methods in treating syphilis of the central nervous system is felt by everyone who comes in contact with large numbers of syphilitic patients in all stages of the disease. The average treatment of syphilis even now with our recently acquired knowledge and new remedies is too often imperfectly carried out. A patient is discharged as cured after a definite amount of treatment regardless of the Wassermann reaction. Or, imperfectly interpreted by the practitioner, the patient is given a feeling of false security because his blood remains persistently negative and the spinal fluid is ignored, although a persistent infection of the nervous system is present with few or no obtrusive symptoms.

One should approach the therapeutic problem in neurosyphilis with an open mind without prejudice and uninfluenced by theories. Clinical and serologic cures are of vastly more value to the patient and to the progress of medicine than *a priori* arguments based on so-called physiologic reasons why they are not possible. None of our present methods of treatment are effective in all cases. Some are cured by intravenous methods alone or combined with mercury. When these methods fail spinal drainage may increase the permeability of the capillaries and lead to a greater penetration of the arsenic. The advocates of the drainage method unfortunately fail to furnish any proof of change in the various phases in the spinal fluid and speak in the most general terms of improvement. It is the old story of clinical impressions and vague statements of great change in the patient's condition without careful and prolonged clinical and laboratory control. I have had the opportunity to examine and treat a number of cases previously subjected to spinal drainage combined with intravenous treatment. In the majority, aside from minor changes in the cytology of the fluid, no improvement was observed. Intraspinial treatment in several of these cases has been followed by negative findings in the fluid and by clinical cures. It cannot justly be stated, therefore, that cures by intraspinal treatment are due to the incidental drainage. I have no brief to offer in behalf of an exclusive method of treatment, and only contend that after failure by the intravenous route we have a valuable procedure in the intraspinal method when used with the proper technic and where indications are present for it.

Condemnation of the method because it fails to cure deep-seated encephalitis and the degenerative stage of tabes is illogical and apart from the thesis I am endeavoring to uphold. My plea is for the use of exact methods in diagnosis which may reveal the early curative stages of neurosyphilis and for proper therapeutic procedures which may then be effective. If physiologic reasons oppose the employment of intraspinal therapy in syphilis of the nervous system they should likewise contra-indicate the use of antimeningitis serum in infectious cerebrospinal meningitis. As curative results are obtained in both conditions, might it not be safe to assume that a revision of the physiologic arguments may be necessary?

Intraspinial therapy is a safe procedure providing the proper technic is employed and judgment exercised in the selection of suitable cases. It is less dangerous than the intensive intravenous method following which severe jaundice, dermatitis or other ill-effects may be seen every day in a large clinic or private practice.

Intraspinial therapy is indicated in all early cases of neurosyphilis, such as meningitis, meningo-encephalitis or meningomyelitis which are not responding to the ordinary forms of treatment. It is contra-indicated, therefore, where there is clinical and serologic response to the intravenous mode of administration and in all cases with nega-

tive findings in the fluid even though clinical symptoms may be present.

In order to minimize the after-effects of intraspinal therapy patients should remain in bed for at least twenty-four hours, preferably forty-eight, and should not be permitted to get up for any reason whatever. Reactions are due (1) to the withdrawal of the fluid and may come on within a few hours in the form of headache—frontal, occipital or generalized—sometimes accompanied by vomiting; or the symptoms may be delayed until the patient is up and about for an hour or more, when headache or pain in the back of the neck or between the shoulders may supervene. These disappear on the resumption of the recumbent position. Patients with lumbar puncture headache should be kept in bed for several days, otherwise the headache may persist for two weeks or more. (2) As the result of treatment patients may complain of pains in the legs, sometimes of the back. They vary in severity from slight, transient pains to severe lightning-like pains. They are seldom met with in early cases but occur more frequently in tabetics, and require the use of opiates during the night, usually passing off the next day, although they may persist for several days. They should be taken as a guide to regulate the dosage and the interval: in patients who are treated at too close intervals, or if the serum is fortified with too large a dose of arsphenamin, anesthesia of the penis or rectum or bladder or numbness of the thighs will follow. The patient will state that he can retain urine for a longer time than usual and that he has movements without realizing that the rectum contains fecal matter. These symptoms are to be looked upon as a danger signal and treatment discontinued and not repeated until the condition has entirely cleared, when only the Swift-Ellis method should be resorted to. Weakness in the lower extremities and even complete paraplegia may result from too frequent repetition of the injection or the addition of too great a dose of the drug in reinforcing the serum.

It may appear superfluous to insist on accurate knowledge and experience before undertaking the procedure in question, but too much emphasis cannot be placed on such fundamentals. Every now and again reports come to me of partial or complete paraplegia and even death following intraspinal injections. It would seem as logical to blame cataract operations by the inexperienced for loss of vision as to incriminate the method in question wrongly employed for these disastrous results.

How long should antisymphilitic treatment be continued? In the absence of toxic drug symptoms and with proper rest periods the treatment may be continued until the blood and spinal fluid become negative. The dosage should be regulated by sex, age, body weight and occurrence or absence of reactive phenomena. It is better to err on the side of safety by giving too little rather than too much. The intervals for intravenous administration should be not shorter

than a week for the majority of patients, in some cases ten days to two weeks. Intraspinally never oftener than every two weeks for the first three or four injections, then at longer intervals. After six or eight treatments a rest period of two or three months.

After an experience of nearly seven years with both the Swift-Ellis and the reinforced serum it has been found that the former introduced by gravity is the better method and is followed by less reaction. The addition of $\frac{1}{4}$ mg. or more of arsphenamin where a number of injections have to be given will in some patients give rise to irritative symptoms, and the addition of smaller amounts has not shown any advantage over the serum obtained after an intravenous injection. It is also important to collect the serum not earlier than one-half hour after the injection. Experiments carried on with blood withdrawn immediately after injection or within fifteen minutes showed the arsenic content to be so high that bladder and rectal disturbances with numbness of the lower extremities resulted. The direct addition of neoarsphenamin or arsphenamin to the fluid is to be condemned (1) because the use of small amounts within a radius of safety is not productive of results, and (2) the employment of larger amounts is an exceedingly dangerous procedure. Small amounts of arsphenamin were used in my clinic over a period of months; and excepting some fluctuation in the cytology the method was barren of any benefit to the patient. The withdrawal of about 16 c.c. of spinal fluid and the medication of 30 to 40 c.c. in the gravity tube with the serum have given the best results.

In neurosyphilis developing within the first year of infection due to a local or disseminated meningitis the most brilliant results are obtained by the combined method. Cases of this nature are met with in patients who have had no treatment or are under treatment. The latter is exemplified in a young girl who had a primary lesion in May, 1919, a macular rash in June and placed herself under treatment in July. The latter part of October, while on a rest period after receiving nine arsphenamin and fourteen mercury injections, she developed a severe unilateral headache which troubled her day and night and would not yield to the administration of various headache remedies. She came under observation again on November 8, when a neurologic examination showed inequality of her pupils, with sluggish light reaction on the left side. The only change in the deep reflexes was in the left patellar, which was more active than the right. Her blood which was negative at the completion of her first course of treatment had again become positive, and a lumbar puncture made on the day of her return showed 16 cells; globulin, 4+; Wassermann, 4+ with 0.6 c.c., and a luetic curve with the gold sol. She was placed on combined therapy and after the second intraspinal injection the fluid became negative and has continued so. She received ten arsphenamin injections, three intraspinal injections and fifteen injections of mercury salicy-

late. Her blood and spinal fluid both became negative, but she was given an additional course of treatment and will remain under observation for the next two years. There have been no further subjective developments. The slight pupillary and patellar differences persist.

Another instance is that of a young soldier treated in the army for a chancre and secondary eruption with ten injections of arsphenamin and a course of mercury. When seen six months later he had a 2+ Wassermann reaction and no neurologic signs excepting a slight inequality of the deep reflexes of the lower extremities. After another course of arsphenamin and mercury he consented to a lumbar puncture. This revealed 15 cells; globulin, 2+; Wassermann, 4+, with 0.6 c.c. and a luetic curve. Under the combined treatment his fluid became negative after three intraspinal injections.

Case 3 is Dr. X., who infected both index fingers while performing a tonsillectomy. Late in April, 1919, the diagnosis of primary lesions was made and treatment immediately instituted. He took seven injections of arsphenamin and twenty-four injections of bichloride of mercury, gr. $\frac{1}{10}$, then potassium iodide up to grs. 60 t. i. d.; after which another course of six injections of arsphenamin, 0.6 gm., twenty-four injections of bichloride and potassium iodide for six weeks. The latter part of September, 1919, he developed intense temporal headache with projectile vomiting. Again he took four injections of arsphenamin, 0.6 gm., and 10 rubs, following which up to January an occasional dose of arsphenamin and mercury and iodide by mouth. At this time he developed an iridocyclitis and received four injections of neoarsphenamin, 0.6 gm.; which had a beneficial effect on the pain and congestion. He came under my observation March 25, at which time it was found he had no vision on the temporal side of the left eye. The left pupil was larger than the right and sluggish to light, otherwise neurologic and physical examinations were negative. His serologic findings and treatment were as follows:

CEREBROSPINAL FLUID.

Date.	Cells.	Globulin.	Wassermann.	Gold sol.	Serum.
Mar. 27, 1920	67	++++	++++ to 0.6	2332100000	April 10, 1920 ±
April 14, 1920	102	++++	++++ to 0.6		
May 5, 1920	15	+	++++ to 0.6	1121100000	
May 26, 1920	7	+	++++ to 1.5		
June 23, 1920	4	=	+++ with 2.0	1111000000	June 23, 1920 ±
July 28, 1920	4	=	~ with 2.0	0000000000	July 28, 1920 -

Treatment from April 8 to July 28, 1920: Five intravenous injections of arsphenamin and five intraspinal injections, Swift-Ellis.

Results. The eye remains the same, the ophthalmologic report being that the floating exudate of the original iridocyclitis is the same in amount and opacity. The vision corrected with a 50-diopter lens has given relief to the headache due to eye-strain.

Many cases of this character might be cited showing the rapidity with which disease of the central nervous system in its inception responds to the combined treatment, necessitating frequently only three to ten intraspinal injections to bring about complete recession of clinical and serologic symptoms. When we compare these results with those after degenerative changes have set in and the Wassermann is practically fixed the value of early treatment is obvious. Speculating as to the future outcome of these patients if a negative Wassermann in the blood alone were depended upon and a *laissez-faire* policy adopted as to the significance of a positive spinal fluid, one can easily visualize them as victims of tabes, optic atrophy, paresis or other types of neurosyphilis.

The following cases of early neurosyphilis treated by spinal drainage are inserted because the first is the only one we have had to date show any decided change in the spinal serology and the other because it shows the usual result with this method.

J. B., aged twenty-eight years. Chancre in November, 1919, followed by adenopathy; no rash. Wassermann, + + + +. After receiving eight injections of arsphenamin and eight of mercury he left the city. In February, 1920, he developed an iritis; a week later, tinnitus and slight deafness. The following week a right-sided facial palsy and two days later paralysis of the left side of face, but not quite so marked. He returned to the clinic on March 16, 1920, at which time a neurologic examination revealed very active deep reflexes on both sides, more marked on the left. There was no clonus or Babinski; slight Romberg was present. His pupils were equal, round and reacted normally to light and accommodation. The right side of the face was paralyzed and the left showed flattening, with weakness of the muscles innervated by the seventh nerve.

CEREBROSPINAL FLUID.

Date.	Cells.	Globulin.	Wassermann.	Gold sol.	Serum.
Mar. 24, 1920	210	++++	++++ to 0.4	5533211000	Mar. 24, 1920 ++++
April 29, 1920	200	++++	++++ to 0.4	2233210000	
May 18, 1920	50	trace	++++ to 0.8		
May 29, 1920	5	trace	++++ to 1.5		
June 16, 1920	4	trace	++++ to 1.5		
July 3, 1920	4	trace	++++ to 1.5		
July 16, 1920	4	trace	++++ to 1.5 1232100000	July 3, 1920 —

Eight weeks after the last drainage the spinal fluid again became strongly positive, showing cells, 200; globulin, 3+; Wassermann, 4+ with 0.1 c.c., and a paretic curve with the gold sol.

Treatment from March 16, 1920, to July 16, 1920: Twelve intravenous injections of arsphenamin; eight spinal drainages, each about an hour after an intravenous injection; ten injections of mercury.

All his symptoms entirely disappeared excepting a slight flattening and weakness of the right side of the face. The amount of globulin in the spinal fluid, although indicated as 4+, was greatly in excess of that usually found, the fluid coagulating almost solid on the addition of the reagents. This rapidly cleared up. To this excessive amount might also be attributed the paretic curve and its rapid conversion to luetic with the diminution of the globulin. The Wassermann in the spinal fluid has not yielded as rapidly as in cases when the serum is introduced.

R. O., aged thirty-five years. Chancre on October 20, 1919; no rash. Wassermann, + + + +. Treatment: eight injections of arsphenamin and eight injections of mercury, when patient discontinued because he could no longer get away from work. About March 25, 1920, he developed severe occipital headaches, which were worse at night. He returned for further treatment on April 7. His pupils were equal, regular in outline and responded promptly to light and accommodation. His deep reflexes were all active and equal on the two sides.

CEREBROSPINAL FLUID.

Date.	Cells.	Globulin.	Wassermann.	Gold sol.	Serum.
April 9, 1920	220	+ + + +	+ + + + to 0.1	5555432100	Nov. 3, 1919 + + + +
April 12, 1920	200	+ + + +	+ + + + to 0.1		
April 26, 1920	100	+ + + +	+ + + + to 0.1		
May 17, 1920	80	+ + + +	+ + + + to 0.1		
June 16, 1920	60	+ + + +	+ + + + to 0.1		
June 28, 1920	50	+ + + +	+ + + + to 0.1	5555432100	June 25, 1920 +

Treatment from April 12 to June 28, 1920: Eleven intravenous injections of arsphenamin; five spinal drainages, each about one-half to one hour after an intravenous injection; six injections of mercury.

Arguments as to the superiority of the intravenous as compared with the intraspinal method are more or less valueless and futile. A wide grasp of syphilis as a general infection, a knowledge of the biologic reactions of the blood and spinal fluid, with sufficient experience to intelligently interpret and correlate them with the signs and clinical symptoms; are essential prerequisites before one is in a position to express a critical opinion.

The results we have obtained during many years of careful work have convinced us beyond the shadow of a doubt that much more

can be accomplished by the method in question in properly selected cases than by intravenous treatment alone.

The group of neurosyphilitics who have been treated intensively by the intravenous method alone with limited or no improvement give some of the best results which have been achieved by intraspinal treatment.

To substantiate this statement the two following cases of optic atrophy are appended:

Dr. Z., a dentist, gave no history of syphilis but had complained of recurring attacks of severe pain in his left eye and back of the neck for several years, the cause of which was not diagnosticated until about a year ago, when he consulted a physician for his failing vision. A Wassermann made at that time was found to be positive as was also his spinal fluid. He placed himself in the care of a competent neurologist and received sixteen injections of arsphenamin intravenously, together with mercury. His vision during the treatment continued to fail until it was lost altogether in the left eye and was rapidly disappearing in the right. He had been obliged to give up his work and could only read very large print in a strong light. A lumbar puncture made on January 24, 1920, revealed 182 cells; globulin, 4+; and Wassermann, 4+ to 0.1 c.c. with a paretic type of curve. On combined therapy his right eye so improved that he was able to resume his profession and also read the paper again. He had seen several ophthalmologists who gave him an absolutely bad prognosis, with complete blindness as the only outcome. On January 14 he consulted Dr. Weeks. A letter from the latter's associate, Dr. Steese, under date of March 8, reads: "Dr. Z., on January 14, showed complete atrophy of the left optic nerve and partial atrophy of the right. Vision of latter was 20/70, left nil. There was no improvement possible." On March 15 Dr. Steese reported: "Dr. Z.'s vision today without glasses: Right eye, 20/50, with -0.75 20/40. This is a great improvement over his visit of January 14, when vision was scarcely 20/70. The left eye can now perceive movements in the outer quadrant." A message from the patient in October stated that his vision continued as in January.

The second patient, aged twenty-eight years, had had a chancre in 1911 followed by secondaries, for which he received a course of injections of gray oil each year. In April, 1918, he noticed gray spots in front of his right eye. Two months later vision began to fail and three months after he was totally blind in the eye. He was treated with arsphenamin intravenously for several months. On February 1, 1919, he complained of cloudiness of vision on the left side. Examination on February 14, 1919, showed the right pupil larger than the left; light and accommodation reflexes absent on the right side; sluggish on the left. Dr. Knapp reported vision 20/30, with temporal contraction of field. His reflexes were more

active on the left side. No Babinski or clonus. Superficial reflexes active. His spinal fluid examined February 18, 1919, showed cells 32; globulin, +++; Wassermann, ++++ to 0.4 c.c.; gold sol, 1233210000. His blood was +++. He was given twelve intravenous injections and eight intraspinal injections along with thirty-five injections of mercury intramuscularly. Owing to the development of jaundice, treatment was interrupted for several months.

Results. On October 15, 1919, Dr. Knapp reported: "While the sight of his only eye remains good there seems to be a contraction of his field particularly for colors on the temporal side." March 2, 1920, Dr. Knapp wrote: "Vision, 20/30; pupil somewhat dilated; reacts slightly; optic nerve pale; vision the same as one year ago." Because of the rapid development of the atrophy in his right eye it is fair to assume that treatment is responsible for arrest of the progress in the left eye. His spinal fluid and blood are negative.

It is poor judgment, to express it mildly, to treat rapidly progressing optic atrophy intravenously without definite knowledge of the spinal fluid. Positive findings, including a high cell count, point to a basilar meningitis, a condition readily influenced by intraspinal medication. Records of twenty cases treated intraspinally show arrest of the atrophy. Why permit such patients to progress to complete blindness when experience shows in certain cases that progress of the atrophy can be absolutely arrested? A patient with a progressive optic atrophy and a positive spinal fluid is not receiving proper or adequate treatment by intravenous therapy alone. Claims made that the remedy cannot reach the diseased optic nerves when introduced in the lumbar subarachnoid space are absolutely untrue and disproved by the clinical results and fluid tests. The first case herein quoted, which is only one of a number of similar ones, had received sixteen injections of arsphenamin intravenously, in spite of which he lost the sight of his left eye and was rapidly losing that of the right; his spinal fluid showed a cell count of 182, indicating that his meningitis was not responding to the treatment given. After two intraspinal injections a decided improvement occurred in the right eye and the cell count was reduced to 22.

Conclusions. A definite and constructive plan for the prophylaxis of the degenerative stage of syphilis of the central nervous system and its treatment in the initial stages can only be devised by a study of the infection in its inception. Our clinical and serological work during the past ten years have enabled us to formulate the following propositions:

1. Syphilis of the nervous system probably begins in the first year of the infection. The number of cases corresponds roughly with the total number of cases of so-called late neurosyphilis. The foregoing statements are based on the following observations and established facts: (a) The number of early cases showing positive

findings in the spinal fluid; (b) familial types of neurosyphilis; (c) biologic evidence of a neurotropic strain of the treponema; (d) persistence of the infection *in loco*, as in aortitis, interstitial keratitis, etc.; (e) observation of patients who developed signs of early syphilis of the nervous system and who after many years died of paresis or other late degenerations; (f) no serologic evidence as yet exists showing normal spinal fluid in the early stage and its infection at a later period.

2. Early neurosyphilis may manifest itself by obtrusive symptoms by slight objective signs or be asymptomatic. Treatment by the usual channels may control the obtrusive symptoms. It seldom cures the underlying infection. Symptoms at times develop during or shortly after intensive courses of arsphenamin and mercury. If not cured these early infections may persist and cause late neurosyphilis.

3. Acceptance of the foregoing propositions leads to the logical deduction that no case of syphilis should be discharged without the knowledge gained by examination of the spinal fluid. In case no evidence of infection is found a prognosis of probable future immunity may be made. If infection exists it should be treated by methods shown by experience to be effective.

4. We are convinced by an experience of seven years in the use of intraspinal therapy that practically all cases of early neurosyphilis can be cured more rapidly, and in the majority of cases only cured, by the combined intravenous and intraspinal method.

THE EFFECT ON BLOOD-PRESSURE AND THE NON-PROTEIN NITROGEN IN THE BLOOD OF EXCESSIVE FLUID INTAKE.¹

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THE nitrogen excretion in nephritis is generally thought to bear a certain relationship to the quantity of urine excreted. Bamberger taught that flushing out the kidney increased the urea elimination. Mohr² in von Noorden's clinic later, concluded that reduction of fluid to the point where the daily output of urine fell below 1200 c.c. often led to urea retention. On the other hand the maximum

¹ Read before the Association of American Physicians, Atlantic City, May 4, 1920.

² Beiträge zur Diätetik der Nierenkrankheiten, Ztschr. f. klin. Med., 1903, 1, 377.

nitrogen elimination was obtained with a daily excretion of 1500 c.c. of urine. Von Noorden strongly urged that excessive quantities of fluid be avoided on account of the danger of raising the blood-pressure. He advised that the fluids be restricted sufficiently to maintain a daily output of 1500 c.c. of urine and as a safeguard once a week a flushing-out day where the fluid intake is increased to the point where the primary output reaches 2 to 3 liters.

This teaching of von Noorden has been quite widely accepted although many have questioned whether the apprehension regarding the danger of raising the blood-pressure by increased fluids was well grounded. This is due to the physiological experiment that in the laboratory animals an intravenous injection of salt solution equivalent to 50 per cent. of the blood volume produced only a slight increase in the blood-pressure. With properly functioning kidneys this probably holds true in man.

Recently, Foster and Davis³ have studied 22 cases of nephritis determining the effect of water drinking on urea excretion. As a result of these observations they concluded, subject to individual variation, that when the daily output of urine was reduced below 1000 c.c. nitrogen retention resulted. The amount of urea excreted increased with the fluid taken and when the urinary excretion reached 2000 c.c. daily the nitrogen output exceeded the intake.

Minkowski⁴ in reviewing the effect of water drinking in gout found considerable difference of opinion regarding its value in the elimination of uric acid. He considered that the maximum benefit is derived when 1½ to 2 liters are taken in the twenty-four hours.

It was thought that it might be of interest to determine whether by increasing the fluid intake to a very high point by use of the Rehfuß tube the nitrogen elimination could be increased as shown by the reduction in the non-protein nitrogen in the blood. At the same time the effect on blood-pressure of high fluid intake could be observed. The observations were carried out on three patients. Two were cases of hypertension. One had only a very slight increase; the other a very decided increase in the non-protein blood nitrogen. Both had nocturnal polyuria and at no time had shown evidence of edema, although both came to the hospital on account of dyspnea on exertion. Apparently they both eliminated water well through the kidney. The urine contained an inconstant trace of albumin, and an occasional hyalin and granular cast. The third case was a typical, chronic gout of ten years' duration. The fingers showed to a very high degree the characteristic deformities. There were urate deposits in the ear cartilages and a large collection of urates in the olecranon bursæ. He no longer had any typical acute exacerbation, but rather prolonged periods of increased discomfort followed by weeks of comparative ease. The blood-pressure was

³ The Effect of Water Intake on Nitrogen Reaction in Nephritis, *Am. Jour. Med. Sc.*, 1916, cli, 49.

⁴ Gicht, 1901.

only moderately elevated, 165 systolic. The urine did not contain any albumin or casts.

During the period of observation all these patients were on the hospital nephritic diet which includes all the carbohydrate foods. In the portions ordinarily served this diet contains between 50 and 60 grams of protein.

The non-protein nitrogen of the blood was determined twice at intervals of four or five days preceding the water drinking test. The mean of these two readings was taken as the average. The water was introduced through the Rehfuß tube, the patient being given $2\frac{1}{2}$ liters every three hours from 9 A.M. to 6 P.M. or a total of 10 liters daily. This was continued for six days and twenty-four hours after completing the test the non-protein blood nitrogen was again determined. The time consumed in taking any one portion of fluid, *i. e.*, $2\frac{1}{2}$ liters, varied from fifteen to twenty-five minutes.

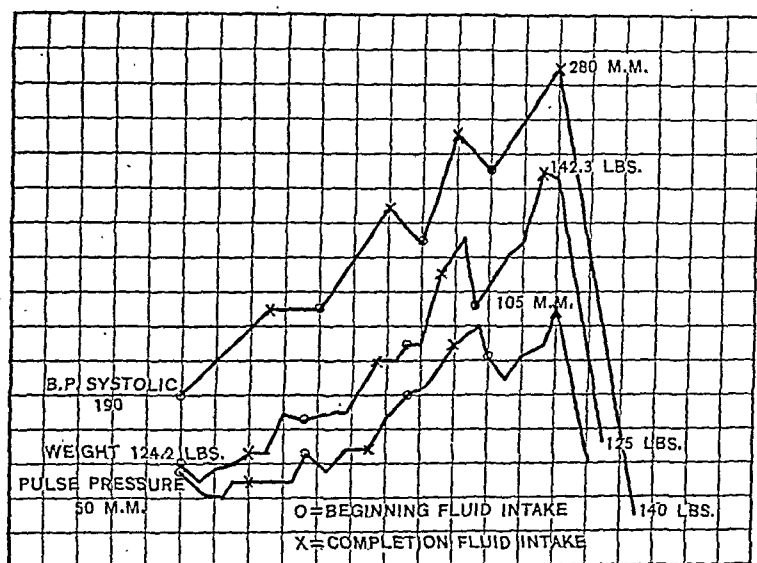
The retention of the water was determined chiefly by repeatedly weighing the patient. The urinary output for the various periods was also recorded.

PROTOCOL I.

	Time.	Systolic.	Diastolic.	Pulse pressure.	Weight, pounds.	Urinary output.
Dec. 20, 1919						
First $2\frac{1}{2}$ liters:						
Before taking.	9.00 A.M.	160	108	52	124.2	
$\frac{1}{2}$ taken . . .	9.15 A.M.	150	100	50	9 to 12 A.M., 850 c.c. clear urine voided.
$\frac{1}{2}$ taken . . .	9.27 A.M.	155	110	45		
$\frac{1}{2}$ taken . . .	9.35 A.M.	158	110	48		
At completion	9.42 A.M.	162	115	47	129.2	
$\frac{1}{2}$ hour later .	10.15 A.M.	162	115	47		
1 hour later .	10.40 A.M.	180	120	60		
Second $2\frac{1}{2}$ liters:						
Before taking.	12.00 P.M.	175	120	55	128.6	From noon till 3 P.M.
$\frac{1}{2}$ taken . . .	12.10 P.M.	180	123	57		1400 c.c. clear, pale urine voided.
$\frac{1}{2}$ taken . . .	12.17 P.M.	180	123	57	
$\frac{1}{2}$ taken . . .	12.22 P.M.	188	130	58		
At completion	12.40 P.M.	205	145	60	134.0	
1 hour later .	1.30 P.M.	205	132	73		
Third $2\frac{1}{2}$ liters:						
Before taking.	3.10 P.M.	210	115	95	132.2	From 3 to 6 P.M., 1575 c.c. of urine voided.
$\frac{1}{2}$ taken . . .	3.20 P.M.	210	125	85		
$\frac{1}{2}$ taken . . .	3.43 P.M.	230	140	90		
At completion	3.50 P.M.	242	142	100	137.5	
1 hour later .	4.40 P.M.	255	150	105		
Fourth $2\frac{1}{2}$ liters:						
Before taking.	6.00 P.M.	225	130	95	136.3	From 6 to 9 P.M. of the next day, 8600 c.c. of urine voided.
$\frac{1}{2}$ taken . . .	6.10 P.M.	230	140	90	
$\frac{1}{2}$ taken . . .	6.17 P.M.	240	145	95		
$\frac{1}{2}$ taken . . .	6.25 P.M.	255	155	100		
At completion	6.35 P.M.	287	180	107	142.3	
1 $\frac{1}{2}$ hours later	8.00 P.M.	280	180	100		
Dec. 21, 1919.	9.00 A.M.	140	90	..	125.8	

I. K., aged thirty-five years, had been in the county hospital repeatedly during the past three years. His chief complaint had been dyspnea on exertion, which rapidly subsided with a moderate degree of physical quiet. His systolic blood-pressure was usually above 200. The maximum reported was 250. There was no evidence of edema. The urine contained an inconstant trace of albumin and an occasional granular or hyaline cast. His phthalein output in three hours was 80 per cent. His urea nitrogen was 24.28 mg. per 100 c.c. of blood. The total non-protein nitrogen was 40.83 mg. Protocol I gives the record for one twenty-four-hour period:

Patient had no bowel movement during the time these data were being taken. At the end of the third five liters he complained of



Showing changes in blood-pressure and weight with each successive fluid intake and the level twelve hours later.

headaches and dizziness, which continued throughout the night. Claims he did not sleep during the entire night because of headaches, dizziness and general depression, with frequent urination. Meals were taken at 11 A.M., 5 P.M., and 8 A.M.

Summarizing the results in this table the systolic and diastolic pressure rose steadily, with the exception of temporary remissions between fluid intake periods from the beginning to the end of the test. The systolic pressure increased from 160 to 287, the diastolic from 108 to 180 and the pulse-pressure from 55 to 107. His increase in weight from the beginning to the end of the experiment was 18.1 per pound. The following morning the weight had fallen to within 1.6 pounds of that preceding the experiment. He first began com-

plaining of headache and dizziness about one hour after completing the second $2\frac{1}{2}$ liters, which corresponds closely to the increase in pulse-pressure. During the other five days of the test he invariably complained of headache at this same period. At no time was there any visible subcutaneous edema. That the volume of the blood was probably definitely increased is shown by the pulse-pressure. The urea nitrogen twenty-four hours after this six-day period of water drinking was 25.5 mg., the total non-protein nitrogen 37.2 mg. as compared with 24.28 and 40.83 mg. before the test. The uric acid was 3.08 before and 1.51 after. The creatinin was 1.56 mg. before and 1.48 mg. after the test. The urea nitrogen actually increased slightly while there was a small reduction in the total nitrogen. These changes, however, may be considered negligible, as they represent only the normal variations. The reduction in the uric acid would appear to have been the result of the treatment, as a week after it was discontinued the uric acid had increased to 2.05. During the week following the patient was given the same amount of water during one night in order to see if the retention of fluids would be the same as during the day.

PROTOCOL II.

Water was given during the night of December 26 and 27, $2\frac{1}{2}$ liters at three-hour intervals as usual, with the following results:

	Time.	Systolic.	Diastolic.	Pulse pressure.	Weight, pounds.	Urinary output.
First 2½ liters:						
Beginning . . .	6.00 P.M.	170	100	70	131.7	6 to 9 P.M., 1180 c.c. pale urine voided.
½ taken . . .	6.05 P.M.	175	105	70		
¾ taken . . .	6.13 P.M.	185	115	70		
At completion	6.25 P.M.	210	120	90	137.2	
2 hours later .	8.00 P.M.	185	115	70		
Second 2½ liters:						
Beginning . . .	9.05 P.M.	190	110	80	134.2	From 9 until midnight, 1800 c.c. of urine voided.
½ taken . . .	9.11 P.M.	195	115	80		
¾ taken . . .	9.15 P.M.	210	120	90		
At completion	9.27 P.M.	220	120	100	139.0	
Third 2½ liters:						
Beginning . . .	12.07 A.M.	180	100	80	134.0	From midnight until 3 A.M., 1950 c.c. urine was voided.
½ taken . . .	12.13 A.M.	205	115	90		
¾ taken . . .	12.30 A.M.	220	120	100		
All taken . . .	12.30 A.M.	230	130	100	138.9	
Fourth 2½ liters:						
Beginning . . .	3.05 A.M.	225	130	95	135.5	3 to 6 A.M., 2760 c.c. voided.
½ taken . . .	3.15 A.M.	225	130	95		
¾ taken . . .	3.19 A.M.	230	130	100	6 to 9 A.M., 1900 c.c. voided.
At completion	3.25 A.M.	260	155	105	140.6	
At	9.00 A.M.	180	105			Noon till 3 P.M., 1330 c.c. voided.
Later	12.00 A.M.	160	100	
Later	3.00 P.M.	140	90	..	133.0	
Dec. 28, 1919.	11.00 A.M.	155	90			

The maximum systolic pressure was somewhat less during the night than during the day experiment (260 as compared with 280). That the water was eliminated much more readily at night is shown by the gain in weight which was 8.9 pounds.

The second patient tested was clinically similar to No. 1, with the exception that the non-protein nitrogen was high. The systolic blood-pressure ranged around 200. The urine contained a trace of albumin and an occasional hyaline and granular cast. The urea nitrogen was 56 mg.; the total nitrogen, 72.9 mg.; uric acid, 6.59 mg.; creatinin, 3.3. On account of the marked distress following 5 liters of fluid the patient was given 7500 c.c. daily the first two days and 5 liters daily the remaining four days.

PROTOCOL III.

	Time.	Systolic.	Diastolic.	Pulse pressure	Weight.
Dec. 2, 1920.					
First 2500 c.c. of tap water:					
Beginning	9.20 A.M.	200	104	96	137.75
$\frac{1}{4}$ taken	9.25 A.M.	198	115	83	
$\frac{2}{4}$ taken	9.36 A.M.	206	96	110	
All taken	9.40 A.M.	204	122	82	142.25
2 hours later	11.30 A.M.	206	110	96	

Patient felt a little dizzy immediately, but it wore off soon. Before the next dose he passed 600 c.c. of urine; sp. gr., 1008 and had a bowel movement.

Second 2500 c.c. of tap water:					
Beginning	12.52 P.M.	208	120	88	142.00
$\frac{1}{4}$ taken	1.00 P.M.	208	110	98	
$\frac{2}{4}$ taken	1.10 P.M.	212	125	87	
All taken	1.16 P.M.	206	140	66	146.00
2 hours later	3.10 P.M.	198	120	78	

Patient was a little restless and dizzy immediately, but no worse than after the first dose. Before the third dose he passed 1200 c.c. of urine of 1006 sp. gr.

Third 2500 c.c. of tap water:					
Beginning	5.00 P.M.	210	125	85	142.50
$\frac{1}{4}$ taken	5.03 P.M.	210	132	78	
$\frac{2}{4}$ taken	5.10 P.M.	220	135	85	
All taken	5.15 P.M.	230	140	80	146.00
2 hours later	7.00 P.M.	242	120	122	

Immediately after this he felt restless and dizzy and complained of a feeling of fulness in the abdomen, but did not seem worse than after the other two doses. However about one hour later he had a severe chill with nausea, vomiting, dyspnea, headache and cramps in his legs. This lasted all night, but by morning he was all right. Urine, 2100 c.c.; sp. gr., 1004.

In this patient the systolic blood-pressure rose from 200 to 242; the diastolic from 104 to 140. The pulse-pressure showed extreme variation, reaching its maximum of 122 at the end of the test. The increase of weight was $9\frac{1}{4}$ pounds. This patient complained of dizziness following the administration of each portion, and one hour after the third portion had a chill with vomiting and cramps in the leg. For this reason no attempt was made to increase the fluid beyond 7500 c.c. The day following the same symptoms following the third portion and in the few following days only 5000 c.c. was given daily. The urea nitrogen before the test was 56 mg.; the non-protein nitrogen, 72.9 mg.; uric acid, 6.6 mg.; creatinin, 3.3 mg. Twenty-four hours after completion of the six days' test the urea nitrogen was 54.1 mg.; the non-protein nitrogen, 69.6 mg.; uric acid, 5.9 mg.; creatinin, 2.45 mg. The slight reduction in the urea nitrogen and total nitrogen is probably negligible as variations of this degree occur normally.

The third patient was a high-grade chronic gout of ten years' duration. His phthalein output was 12 per cent. in three hours. Systolic blood-pressure ranged from 150 to 170.

This patient took 10 liters of water daily for six days without inconvenience. He eliminated the fluid almost as rapidly as it was taken. The maximum increase in blood-pressure was 15 mm. and he did not show any appreciable gain in weight.

The urea nitrogen before the test was 66 mg.; after the test 69.4 mg. Total non-protein nitrogen before the test, 92 mg.; after the test, 97 mg. Uric acid before, 8.25 mg.; after, 4.85 mg.

This shows a very definite reduction in the uric acid, but an increase in the urea nitrogen and total nitrogen. It is highly probable that this reduction in the uric acid was the result of the treatment as repeated determination of uric acid previous to and following the test had never fallen below 6.25 mg. per 100 c.c. of blood. One week after the test the uric acid had increased to 9.17 mg. This is in accord with what occurred in Case I where there was a very definite decrease in the uric acid, but without change in the urea nitrogen. The patient with gout, however, in a later test where he was given 10 liters of water daily for eight days, showed a slight increase in the uric acid in the blood from 6.17 to 7.25 mg. per 100 c.c. Atophan, 3 gms. daily for one week, did not reduce the amount of uric acid in the blood.

We wish to acknowledge the valuable assistance rendered by the interns on the service at Cook County Hospital.

Summary. In patients with hypertension and presumably chronic interstitial nephritis, large amounts of fluids may cause a very decided increase in blood-pressure. Whether this rise occurs depends upon the promptness with which the kidneys function in excreting water.

In the three cases studied the taking of large amounts of fluid

daily for a period of six days was without effect on the urea nitrogen in the blood. As it was not feasible to determine the nitrogen eliminated in the urine during this period these results do not exclude the possibility of increased nitrogen output.

In two of these three cases the uric acid in the blood was definitely lessened. This was probably due to the treatment as following its discontinuance there was an increase to the previous level.

PROBLEMS CONCERNING URINARY CALCULI.¹

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URINARY calculi consist of agglomerations of non-acicular crystals about a nucleus of organic matter. Concentration of the urine in the presence of pus or blood due to trauma or disease must be the occasion of stone formation. But with the exception of the secondary calculi, obviously due to inflammation, this bare fact has not elucidated the cause of stone. One would expect that trauma to the kidney should be a frequent cause of bleeding calculated to result in stone; yet such does not seem to be the case. Prize fighters are not notoriously subject to stone, and in reviewing a series of some 200 cases of primary renal stone, I find but 5 in which the symptoms of stone began within a few years after a trauma.

It is more profitable then to accept the fact that stones do begin and to study the clinical features they present that seem to bear upon their origin.

Most primary stones contain both urates and oxalates. But in contrasting bladder and renal calculi we are immediately struck with the predominance of urates in the stones found in the bladder and the predominance of oxalates in renal and ureteral stones. By the same token the former frequently fail to show by roentgen ray while the latter are but rarely overlooked. Thus in a consecutive series of cases in which stone was present the radiographic results were as follows:

	Positive.	Erroneously negative.
Renal pelvis	32	6
Ureter	20	14
Bladder	16	12

Most of the failures to show ureter stone are attributable to the small size of the stone and many of the successful pictures of bladder stones to the presence of phosphates.

Bladder stones are disproportionately frequent in childhood, corresponding with the predominance of urate deposition in the

¹ Read before the Association of Genito-Urinary Surgeons, May, 1920.

urine of the young, while adults show a more marked tendency to the urinary precipitation of oxalates.

A majority of the urate stones retained in the bladder have no antecedent history of renal colic. Does this mean that urate stones more commonly form in the bladder while oxalate stones more often form in the kidney pelvis? Probably not. Let us not forget that the urologist is not really concerned with stone as such but only with such stones as fail to pass from the urinary channels or in passing excite symptoms. Many very small stones doubtless pass silently. We are interested only in those that grow so large they cannot do this. And this means retention.

There are four ways in which a stone may be retained in the urinary channels, viz.:

1. The stone may adhere to its point of formation until too large to pass.

2. It may be irregular in shape and thus peculiarly liable to catch in ureter or urethra.

3. It may lie in some part of the pelvis of the kidney or bladder where it does not present at the ureteral or urethral orifice.

4. There may be ureteral or urethral obstruction (*e. g.*, stricture).

1. *Adhesion to the point of origin* may be actually observed in the case of secondary bladder stones. A similar process may delay the discharge of certain primary renal stones, for sometimes we recover small oxalate stones (after they have passed noisily down the ureter) which show a cup shape, as though they had remained for some time adherent to the tip of a renal papilla; indeed, such adhesion has been observed postmortem.

2. Comparison of the size and shape of stones passed after renal colic with the difficulty of their passage will confirm the rather obvious assumption that *it is the shape rather than the size* that determines the likelihood of the stone being caught and temporarily or permanently impacted in the ureter.

Is not this the reason why we, who are interested only in impacted or retained stones, find oxalates predominating in the upper and urates in the lower urinary channels? It would seem so. At least I know of no change that the urine undergoes in passing from the kidney to the bladder that would make it more likely to form urate stones in the latter while the smooth urate stone may certainly slip silently down the ureter that would react in violent spasm to the passage of a jagged oxalate stone even smaller in size. But once the stone reaches the bladder the probabilities are reversed. Here the very roughness of the oxalate stone facilitates its discharge by exciting contractions that no smooth stone would evoke.

3. *Retention* explains several facts in relation to stone. The silent stone filling the pelvis of the kidney has had its beginning as a small stone lying in one of the lower calices until it has grown over the orifice of the ureter. Such silent stones are also found in the

bladder and even in the ureter and the urethra. In the bladder they imply, at least a little retention of urine (perhaps the same is true of the kidney) and in the narrow passages the silent stone is usually found behind a stricture.

By means of the roentgen ray I have actually watched the growth of a secondary renal stone (whose rate of growth is much more rapid than that of a primary stone) in seven years from a maximum diameter of 0.5 cm. to 5 cm.; and in my precystoscopic days I watched a patient, who suffered only from a slight hematuria when he rode horseback, for three years before the roentgen ray revealed two stones in his bladder, each of them 3 cm. in its smallest diameter.

In the ureter I have known a stone to cause a severe colic and then remain entirely silent for five years. Another ureteral stone (following trauma to the loin) produced attacks of pain of varying severity for fifteen years (approximately) and thereafter for twelve years only hematuria when the patient rode horseback. Another grew to be 1 cm. long and never gave a symptom.

In the urethra I have known a stone to grow (behind a tight stricture) to a size almost that of the last joint of the thumb without exciting a symptom of which the patient was willing to complain—indeed, he entered the hospital for the treatment of rheumatism and his stone was disclosed by the routine examination.

Perhaps the best testimony to the influence of retention upon stone is the fact that I have never seen a primary stone retained in the bladder of a woman and but one in the female urethra.

Renal Colic.—The following table collected from my case records shows the age at which the first colic or pain proved due to ureteral or renal stone was felt:

Age at first colic.	Cases.
Birth to 10 years	6
11 to 15 years	1
16 to 20 "	13
21 to 25 "	21
26 to 30 "	30
31 to 35 "	28
36 to 40 "	32
41 to 45 "	20
46 to 50 "	21
51 to 56 "	17
57 to 60 "	7
61 to 65 "	3
66 to 70 "	0
71 to 75 "	2
Total	201

This table may be summarized by the statement that only one in ten of the patients began to have renal colic before the age of twenty, yet one-half had begun before thirty-five; the peak is between the ages of twenty-six and forty; the odds against beginning to have renal colic after the age of fifty are about twenty to five.

These statistics were gathered from 244 patients proved to have urinary stone, presumably primary in the kidneys. In 225 there was evidence (pain) that the stone had originated in the pelvis of the kidney. There were only 11 cases of "silent" stone (two bilateral), 3 with only mild pain and bleeding and 5 with toxic symptoms exclusively.

Having a distinct impression that the mobility of the right kidney should make renal colic definitely more frequently upon the right side, I was disappointed to find, after tabulating 178 cases, that 90 occurred upon the left and 88 upon the right side. The statistics of Braasch and of Cabot confirm this observation.

But we are more immediately interested in the practical questions relating to renal colic. When a stone jams in the ureter, what is the best method of relieving the colic and of expediting the passage of the stone? How shall we know that the stone will not pass? And if the jam is thus permanent, in what portion of the ureter is it most likely to occur?

There seems to be a general impression abroad that colic expedites the passage of stone through the ureter. At any rate we commonly speak of the passage of stone following a colic. Yet, considered as a mechanical proposition, a renal colic is rather the outcry of the outraged, overdistended urinary channels than a coördinated effort to expel a foreign body. It may conceivably benefit the sufferer little more than a cramp in the leg does a swimmer. It would be more accurate to look upon the cessation of colics as the evidence of the passage of stone. Commonly the stone seems to leave the ureter with a colic, but close observation will bring to one's notice many instances in which the stone leaves the ureter without a colic. I have observed two very striking examples of this, in each of which the stone passed without colic, and indeed under conditions that precluded the possibility of colic. And these stones were above the average in size.

CASE I.—The patient was a stout, middle-aged Russian who had paid as little attention as possible to the renal colic from which he had suffered for several years. Finally his infected renal pelvis ruptured, but even then he did not call a physician until he was so nearly dead from sepsis that the first surgeon summoned to his bedside deserted him, with the cheering information to the family that the "patient would be dead by morning." But the infection was an acute one and the patient a sturdy type. I drained his loin, he recovered and is alive and at work today, though suffering from renal insufficiency, it being now fifteen years since the operation. But the startling feature of his case is that on the fifth day after operation he passed from his bladder a stone, 1 x 2 cm. in diameter. The kidney was draining freely into the loin at the time and he had not the least ureteral pain to announce the passage of the stone, though it passed through the urethra with some difficulty.

CASE II.—A similar case. I was called out of town to operate upon a man who after a single renal colic had been in calculous anuria for several days. Bilateral simultaneous nephrotomy drew several stones from the left renal pelvis. The right yielded only urine under great pressure. It was deemed safer not to attempt any further exploration; yet on the sixth day of his uneventful convalescence he passed a stone about 0.5 cm. in its smallest diameter and without any ureteral colic. Subsequent radiograms were negative and he had no further symptoms of stone in the two years that elapsed before I lost sight of him.

Since these two cases called my attention to the possibility of the passage of ureteral calculi without pain I have confirmed the observation several times.

CASE III.—Thus last summer I took charge of a woman who having lost her right kidney the year before (nephrectomy for stone) had been in bed for several weeks suffering from urinary septicemia, with recurring chills and fever and loin pain of considerable severity. I promptly transferred her to a hospital, where the roentgen ray revealed a small stone at the lower end of the left ureter. I thereupon by abdominorectal palpation felt the stone and endeavored to dislodge it. Neither she nor I believed I had accomplished anything, but when I visited her the next day her temperature was down, the loin pain had ceased and she assured me that she felt the stone in the bladder. The following day she passed it. She remains well today (a year later).

Such observations as these suggest that a stone—even a large stone—may pass from the ureter without colic. They also suggest, as previously stated, that the colic is comparable from various points of view to the cramp in the leg of a swimmer.

What then should we do in the presence of renal colic? Kill it. I have tried to do this with various of the substitutes for morphin. None of them has given me any satisfactory results. General anesthesia is the only competitor. I have no reluctance about giving the drug freely. One of my interns took 25 minims of Magendie's solution one night before he got rid of his renal colic; and he seemed little the worse for wear the following day. In short, I advocate the administration of morphin, not out of sympathy for the patient's suffering but because it relieves the spasm that is surely doing little good, may do harm and without which the patient can perfectly get rid of his enemy.

Among the mechanical aids to the passage of ureteral stone I cannot name one for which I have any very great preference. If the stone is at the lower end of the ureter I always attempt to help it along by recto-abdominal manipulation, and have thus twice delivered stones into the bladder. I have had no success with the various fluids recommended for injection into the ureter, and the

only ureteral operation that has shown any promise in my hands is one I hesitate to recommend, as it seems so fantastic. If the stone is arrested near the lower end of the ureter, even though it be several centimeters from the bladder orifice of the canal, I believe its ultimate expulsion is expedited by cutting open the urethral orifice with the cystoscopic scissors or forceps. The ureter catheter itself, of course, occasionally dislodges a stone. I believe that I have eight times expedited the passage of ureteral stones by mechanical measures.

How shall we decide that a stone is permanently lodged in the ureter? This, the most important of all the problems in relation to the surgery of ureteral stone, cannot be answered categorically.

CASE IV.—I was once consulted by a patient who was most anxious not to be operated upon for six months, although the roentgen ray had shown a small stone in the upper part of his right ureter.

His only colic had occurred the week before. It seemed possible that the stone would pass, and inasmuch as the ureter catheter not only verified the location of the stone, but also showed that the kidney was not infected and was functioning as well as its fellow, I felt justified in countenancing the delay, leaving him in the hands of his brother, a physician. The next news I had of the case was three months later a telephone message at 1 A.M., stating that after a colic of five days' duration he had ceased to urinate. I found him delirious, febrile and anuric. Incision of the loin revealed an impacted stone, a ureter so gangrenous that it ruptured as I picked it up and a large perirenal collection of urine and pus. I ventured to do a nephrectomy and the patient was fortunate enough to recover though he lay desperately septic for many weeks and did not leave the hospital for three months. In the five years since operation he has passed a stone from his remaining kidney, and he is now suffering from chronic nephritis and high blood-pressure.

In this connection it may be worthy of note that the ureter may be obstructed by crystals, there being no actual stone formation. The type of renal colic that follows a good dinner and a shower of crystals is doubtless not unfamiliar to you. I once cured a renal colic by liberating a bunch of such crystals jammed in the ureter, through poking them with a ureteral catheter. One of my patients got into a much tighter place, as follows:

CASE V.—A pale, thin boy, aged seven years, had long been subject to renal attacks (not recognized as such) characterized by fever and vomiting. These attacks were usually relieved by calomel. On the morning of October 23, 1913, he passed some urine containing grit, and thereafter ceased urinating for four days, at which time he came into my hands with bilateral loin tenderness

but no pain, considerable abdominal distention, a pulse of 100, blood-pressure 140, temperature about 100°. I opened both of the pelves of his kidneys and decapsulated the kidneys in twenty-five minutes. The urine was under great tension and was muddy with urate crystals, but no stone was found. The pelves were flushed out and left open. After two weeks of tardy convalescence his loins healed, though ten days later the left one reopened for three days. Roentgen rays were negative after the operation.

Since that time his mother has been a little more prompt in giving him calomel. The urine remained purulent for two years and he still has a trace of albumin, but no casts and no pus, seven years after his operation.

I have searched the records of some 200 cases of renal pain due to stones in an effort to find how long it is possible for a stone to remain in the ureter and still pass without permanent damage to the kidney. Inasmuch as six months appears to be the accepted limit for awaiting the passage of stone after a renal colic, I have enumerated only those that went longer than this without gravely impairing renal function, as follows:

	Cases.
9 to 12 months	5
12 to 18 "	3
18 to 26 "	6

These facts are recorded for edification, not as a guide to practice. They illustrate the extremes, neither of which may be our guide.

Doubtless we may agree that operation for ureteral stone should be advised under three conditions, viz.:

1. Because of the alarming symptoms excited by the stone.
2. Because the stone does not progress and cannot be made to progress by manipulation.
3. Because the stone is more than 0.5 cm. in diameter.

Or perhaps these three reasons might be summarized by the statement that the shape of a ureteral stone determines its fate.

The rounded stone, largely composed of urates or phosphates, produces relatively mild colic and its passage may be awaited with some complacency if it engages in the ureter before it reaches a diameter of 1 cm. But any one who has enjoyed the passage down the ureter of a jagged flake of oxalate crystals so small as to be almost invisible to the roentgen ray will agree that words fail to do justice to the discrepancy between the size of the enemy and the distress it can cause. One can usually judge the shape of the stone with a certain degree of accuracy by the shadow it casts and the depth of the scratch it produces upon the wax bulb. Exceptionally, however, stones escape diagnosis not only by the roentgen rays but by the wax bulb as well. I have three times failed to identify a small stone in the ureter by the wax bulb. One of the cases is so deplorable that it is worthy of contemplation.

CASE VI.—The patient came from out of town for a diagnosis. He had suffered from pain of moderate severity in the right side for three months. The pain suggested renal colic and was accompanied by the passage of blood, either microscopic in quantity or just sufficient to make the urine smoky. When he reached New York his pain had ceased and his urine showed nothing abnormal beyond a trace of albumin and a few leukocytes and red cells. Physical examination revealed nothing wrong. Ureter catheters obtained urine equal in quantity and quality from the two kidneys. Wax bulbs showed no scratch although the catheters went readily to the kidney pelves. A pyelogram was negative. So I sent him home with the statement that he had doubtless passed a small stone without noting its passage from the bladder (this often occurs). Within a week he was back with smoky urine and a little pain. Instead of reexamining him, as I should have done, I performed the operation that never succeeds in my hands—exploration of the kidney for a diagnosis. On finding the organ normal I even split it from end to end (an operation I had performed but once before and which I believe I may safely promise never to repeat). Result: Zero. I passed a catheter down the ureter to the bladder. This revealed nothing. So I sewed up his kidney no wiser than I had been. He became infected and septic. Pneumonia followed, then empyema. Finally, as he was recovering, he passed a small ureteral stone—and I got the idea.

He has remained well for three years now, and, I am proud to state, considers me a wonderful surgeon who saved his life.

In such a case as this nothing can save the diagnosis except an unflinching clinical conviction that in the face of symptoms suggestive of renal stone no negative evidence is worth consideration. I wonder how many of the cases of renal pain or bleeding that are relieved by a negative exploration of the loin are not actually cases of small ureteral stone undiagnosed.

But this difficulty of diagnosis applies only to the smallest stones. The others will show, will scratch, will give secondary changes such as dilatation discoverable by pyelography and ureterography, deficient renal function, infection. Indeed a proper diagnosis covers all of these points and ensures their correspondence. One cannot too often remind one's self that the complete clinical picture must include not only a set of statements from the patient, all of which point to the same diagnosis, but a contributory set of data elicited by the more specialized methods of diagnosis. I know no case better calculated to offset the one last related, in which an unwarranted exploration of the kidney almost resulted in the patient's death, as the following, in which the reluctance to exhaust every means of diagnosis, including a surgical exploration, combined with a lapse of clinical acumen to prevent a diagnosis that might have saved the patient's life.

CASE VII.—This patient had as his only symptom infrequent hematuria of such severity as to suggest neoplasm. The roentgen rays showed a shadow suggestive of a large stone impacted in the ureter at the brim of the pelvis. This was, alas, before I was using the wax bulb, and cystoscopy and ureter catheterization revealed nothing abnormal. No renal deficiency; no pus or bacteria; no impediment to the passage of the ureter catheter. I should have known that he did not have a stone in his ureter, but I did not. I operated and removed an enterolith from the much dilated vermiform appendix, which was sunk in an adherent coil of small intestine with which it communicated by many openings. I solaced myself with the possession of an interesting specimen and the fatuous theory that this stone might have caused the hematuria.

The patient disappeared for three years and then returned, stating that his hemorrhages had recurred from time to time, latterly with such severity as to cause clotting in the bladder. He had suffered some discomfort in his right loin, but I could not palpate his kidney, and ureter catheterization and roentgen rays were again negative, the right kidney showing plainly and being apparently normal in function, size and shape. As three years had elapsed since the beginning of his bleeding I relinquished the theory of neoplasm which was obviously suggested and once again dismissed him undiagnosed.

This time he returned in a year, emaciated, his loin full of neoplasm, inoperable to the extent that he died of my effort to remove the kidney which lay upon a bed of carcinomatous glands as big as itself.

May the recital of these woes prove as profitable to you as I believe they have been to me.

Bilateral Stone and the Single Kidney. The problem of stone in the kidney that is supporting the patient's life appears under various forms. We may enumerate the following:

Stone on one side and renal insufficiency on the other:

Due to stone (*i. e.*, bilateral stone).

Due to other diseases of the kidney.

Due to congenital deficiency.

Due to urethral retention.

Stone in a single kidney:

Atrophy of the opposite kidney due to disease.

After removal of the opposite kidney.

Fused kidney.

Non-development of the opposite kidney.

This great variety of conditions from stone in both kidneys to stone in the one kidney the patient possesses, presents the common problem of the influence of disease or absence of the opposite kidney upon the treatment of renal and ureteral stone.

Bilateral Stone. This type condition of bilateral surgical renal disease may exhibit various degrees of unilateral or bilateral renal deficiency, but its most interesting phase is that in which the patient complains of unilateral symptoms and examination reveals gravely deficient renal function due to large or multiple silent stone in the opposite kidney. Under such conditions the following rules for operation are doubtless generally acceptable:

1. The kidney showing the better function should be operated upon first.

2. The kidney showing acute symptoms is usually the sounder organ.

3. Impaction of stone in the ureter of the sounder kidney may temporarily reduce its function below that of its fellow. Under such conditions it is safer to operate first upon the side with ureteral stone.

4. Simultaneous bilateral operation may be attempted if the patient's condition is relatively good and the first operation not unduly long (thirty minutes).

5. In an emergency, such as anuria, the sole object of operation should be to provide drainage to the kidney, usually by pyelotomy (which in case of anuria should always be bilateral). Such stones as cannot be rapidly reached and readily removed should be dealt with at subsequent operation.

6. Geraghty's formula, *i. e.*, good concentration of urea and of phenolsulphonephthalein and a small quantity of urine (with consequent low total 'phthalein) may be depended upon to indicate an atrophied or congenitally small kidney inadequate to support life. I have twice correctly diagnosed unilateral renal deficiency of this nature by the Geraghty formula. My impression has been that bilateral renal stone is very common. I have been surprised to find how few are identifiable among my cases.

I have classified as follows the cases in which the data were sufficient to permit of accurate classification:

Total cases	187
Bilateral	49
Total kidneys involved	236

The calculous crop from these kidneys was distributed as follows (estimates are per kidney, not per stone. Thus if a kidney gets rid of four stones and retains one, only the retention counts):

Stone retained in the pelvis of the kidney	95
Stone permanently arrested in the ureter.	60
Arrested in the bladder	21
Arrested in the urethra	3
Stone passed	68
	247

The duplications were as follows:

Pelvis of the kidney and bladder	8
Pelvis of the kidney and ureter (same side)	3
	11

Many of these data run contrary to my preconceptions. Are not more than 25 per cent. of stone bilateral? Are not more than 4 per cent. of calculi arrested in both bladder and kidney pelvis? If 60 stones were arrested in the ureter, did not more than 68 kidneys succeed in passing all their stones? Is it true of stone-bearing kidneys that one-third of them retain at least one of their stones, that one-quarter more do not get all of their stones down the ureter, that from 10 per cent. the stones are retained in bladder or urethra and that only a little over a quarter pass all the stones they make?

But one of the most interesting problems in prognosis these figures do not even hint at. We see most of these cases after they have had a renal colic. Our clinical resources permit us to say with a fair degree of accuracy that a patient who has had a renal colic is or is not free from stone. If he is can we guarantee him against another renal colic? Obviously not. We can do nothing except to treat infection if such exists. Well then if he may have other colics are they going to threaten him more than the first one? My records only answer by failing to show a case where a kidney that passed its first stone successfully, failed to pass the subsequent ones as well. Can this be the general rule? I hope so. At least I am encouraged to tell my patients and myself that a renal colic successfully weathered is the best possible insurance against retention of stone. It means that the kidney drains well, lets its stones escape early.

Silent Stone. My list of silent renal stone cases is the following:

	Cases.
Unilateral silent stone	9
Bilateral silent stone	2
Silent on one side, symptoms on the other	11
	<hr/> 22

The following cases illustrate extremes in the histories of silent stones:

CASE VIII.—An indolent, wealthy, heavy drinker. At fourteen years of age he passed a stone after a colic. At fifty he was found to have pyelitis. At fifty-five he began to suffer from neuralgia of the thighs, doubtless due to renal insufficiency. At fifty-eight he began to have mild attacks of hematuria. These continued until at the age of sixty-three he had a severe one, lasting several months. He lost twenty-five pounds in a year and came to me for a diagnosis. The roentgen rays showed his kidneys to be widely distended with stones and one small one stuck at the upper end of the right ureter. After five months of bleeding he passed this stone, regained most of his weight and is now surprisingly active at the age of sixty-seven.

CASE IX.—A Russian Hebrew. At eight years of age he had a hematuria. At fourteen he passed a stone. At nineteen litho-

lapaxy (in Russia). At twenty-four he entered Bellevue Hospital septic and with his first renal colic. He passed his stone and I removed large stones from both kidneys simultaneously. He was comparatively well, but with a mild infection of both kidneys when I last saw him six months later.

CASE X.—Entered hospital with as alarming a renal colic as I have ever witnessed. The temperature on admission was 105°. The right loin was intensely sensitive and rigid. Roentgen rays showed the left kidney full of stones, but nothing on the right side. Within twenty-four hours the temperature fell to normal, but the right kidney remained so large and tender that the initial diagnosis of perinephritic abscess was adhered to by certain members of the staff. Meanwhile he was cystoscoped, the left renal deficiency confirmed and a small stone was seen in his bladder. This had evidently caused the right renal colic. He was kept in the ward two weeks while the congestion of the right kidney subsided, after which I successfully removed the left one, finding it completely destroyed by calculi. The stone seen at the first cystoscopy passed painlessly from the bladder and was lost.

CASE XI.—A sedentary business man; rather stout. At eight years of age he had a stone removed from the bladder. He recognized no further symptoms of urinary disease until, at the age of forty-seven, while playing golf, he did one of those things that to the non-golfer are mystery—sprained his back so badly that he had to give up his game. By the time he got home his loin was both swollen and tender. A few days later a physician opened it, letting out a large quantity of fluid blood. After this he was comfortable and able to resume his work, but the incision did not heal and after a while it was discovered that the slight discharge from it contained urine. Roentgen rays showed a kidney full of stones. He refused operation, and three years later he writes me that he still has his little fistula but is otherwise entirely well.

The symptoms of calculous anuria are familiar, as are those of rupture of the pelvis of the kidney. I have operated upon each four times. Two of the anuria cases died, the others recovered, as did all four rupture cases.

The common feature of silent stone cases is that their silence is an ominous one. Whether in kidney, or bladder, the more prolonged the silence the more impairment of renal function has resulted and the greater the danger from any operation.

On the other hand the removal of small silent stones is indicated as a prophylaxis of the very renal impairment that results from their neglect. Such stones as may be removed without tearing of the renal substances should be operated upon after they have reached 2 cm. in diameter.

Stone in a Single Kidney. Let us extend the term "single kidney" to its widest physiologic limit and include not only those cases in which the opposite kidney is anatomically absent but also those in which it is merely physiologically incompetent to support life. May we not conclude that such a condition constitutes a surgical emergency? If the stone is impacted in the ureter of a single kidney it immediately and obviously threatens life; if silent the threat is less immediate, but none the less obvious. Stone in a single kidney not only may but must be operated upon, unless there is some other contra-indication to operation.

I have operated upon several such cases, the result of operation depending more than anything else on the degree of chronic renal deficiency due to prolonged suppuration. My most interesting and brilliant case was the following:

CASE XII.—An able-bodied Irish laborer, whose previous history contained nothing relating to his urinary organs, sat for two hours on a board covered with ice, in February, 1915. Within a few hours he had a severe pain in his left loin, and the next day did not urinate. Alarmed at this he consulted a physician, who passed a catheter but obtained no urine. Meanwhile the pain had disappeared and the patient felt perfectly well. So for six days he did nothing, though during that time he passed not a single drop of urine. He then entered St. Vincent's Hospital.

He said he felt well but he was mentally a little stupid, his superficial capillaries a little congested, his intestines distended, his blood-pressure 170, his temperature normal, his left loin slightly tender, but owing to distention the kidney could not be felt.

The roentgen rays showed a large left kidney but no stone. The cystoscope showed a congestion of the bladder vessels corresponding to the skin congestion. There was not a drop of urine in the bladder. The ureter catheter went 30 cm. up the left ureter, but drew no urine. A filiform ureteral bougie entered the right ureter for only 5 cm. and drew no urine.

I therefore immediately cut down upon the right loin but found no kidney there. I turned him over and opened the left loin and found the left kidney very large, congested and tense. I incised the cortex and pushed a tube into the pelvis of the kidney, liberating an ounce or more of urine.

For two days he was semicomatose and then recovered and made a brilliant operative recovery. For three weeks he passed large amounts of urine daily from the loin tube but none from the bladder. From the bladder washings streptococci were obtained. A second cystoscopy revealed nothing new. Then he began to urinate as much as 700 c.c. in twelve hours. I therefore removed the tube and in a week the sinus closed, whereupon the temperature went to 105° and the loin reopened, so I replaced the tube and left it in.

In July, five months after the first operation, he returned to the hospital, still passing all the urine through the left loin. I reopened the loin, found the kidney very adherent and the sinus entering the center of the cortex. I mobilized the lower pole subcapsularly, disclosed the adherent pelvis and the ureter moderately dilated below a narrow tight stricture at the ureteropelvic junction. I opened the ureter and found that I could not pass even a probe through the stricture. I hoped to do a plastic operation, but found that I could not mobilize the ureter or the kidney sufficiently to do so. I therefore made another incision an inch down the ureter and introduced a 20 F. catheter through this up into the pelvis of the kidney, thus splinting the stricture wide open. This tube was left in for three days. Thereafter most of the urine came from the urethra, but four days later his temperature rose to 104° and remained thereabouts for three days, when he passed a small phosphatic stone. His loin then promptly healed and his convalescence thereafter was uneventful.

Two years later, in July, 1917, after a week of pain and fever in the left loin, he returned. I watched him for ten days, during which he had irregular fever, each relapse of temperature being accompanied by pain in the loin and definite anuria, the longest period of anuria being twenty-four hours. Roentgen rays showed three shadows in the region of the left kidney, two of them regarded as stones. I opened the loin for the third time, found the kidney so bound down that I could hardly budge it, opened it through the old nephrotomy wound and found but one stone, stuck in the orifice of the perfectly patent ureter. The convalescence was entirely uneventful except that I had to irrigate the pelvis of the kidney once through a ureter catheter to reestablish ureteral drainage.

In 1921, five years after his first operation, he remained entirely well, at work and weighing 200 pounds, but I have had no opportunity to make any examination, except to look at his urine, which showed no pus to the eye.

Infection and Stone. One may well admit the many difficulties that surround the complete cure of the infection so often associated with renal and ureteral stone. A *Bacillus coli* infection we look upon with a philosophic calm. It is at least not likely to occasion a relapse of the stone. But the cocci do occasion relapse even in kidneys that are seemingly draining well. Fortunately the cocci are particularly vulnerable to antiseptics by hexamethylenamin.

In this connection it may be stated that the frequent occurrence of epididymitis as a complication of renal stone with cocci infection is not without clinical significance. It means at least that the internal genitals are infected. One will of course find pus in the prostate and vesicles. I have taken this hint and in several cases succeeded in clearing up an otherwise intractable postoperative coccic infection by combining urinary antiseptics and massage of the

internal genitals. Lavage of the renal pelvis, on the other hand, has given me no better results than might be expected from the catheterization.

In short the following routine may summarize my views on the treatment of renal infections associated with stone.

1. In operating maul and tear the kidney as little as possible.
2. Assure drainage by dilating ureter strictures widely, and if it seems wise, by fixing the kidney high in the loin.
3. Symptoms suggesting renal retention occurring while the loin fistula is still open call for immediate irrigation of the kidney pelvis through the ureter catheter.
4. During convalescence, hexamethylenamin and bladder irrigation as a routine.
5. The source of infection may be in the tonsils, teeth, bowel, etc., and an effort should be made to get rid of it.
6. The prostate should not be forgotten.
7. Use the wax bulb as a routine to detect the presence of stone or stricture of the ureter even when one does not expect to encounter them.

Operative Statistics. I have performed eighty operations for stone in the kidney pelvis and ureter. They may be classified as follows:

NEPHROTOMY.

- 24 cases (1 bilateral).
- 12 cases, of which 4 were known to remain well one to two years after operation.
- 10 incomplete or relapsed, of which 1 cured by second nephrotomy six years later.
- 2 cured by secondary nephrectomy.
- 1 died after secondary nephrectomy.
- 2 died—1 by renal insufficiency and 1 by sepsis.

NEPHRECTOMY.

- 33 cases, 22 recovered.
- 11 died, of which 2 were from pulmonary tuberculosis, the kidney being tuberculous as well as calculous; 2 septic, the opposite kidney being apparently sound at the time of operation; one of these was a secondary nephrectomy. In both the patient was gravely septic at the time of operation.
- 1 post-operative ileus.
- 1 uremic, from chronic parenchymatous nephritis.
- 2 septic (bilateral stone).
- 3 of renal insufficiency (bilateral stone).

PYELOTOMY.

13 cases (3 bilateral); 1 died, 3 remained severely infected, 1 stone relapsed, 10 cured, and in 8 cases the cures persisted for three years or more.

URETEROTOMY.

17 cases. No deaths. In 3 no stone was found. In 2 of these the stone was subsequently passed, one required subsequent nephrectomy for a cure. 2 relapsed.

Negative exploration of loin for stone—3 cases. All recovered.

The conclusions that may be drawn from this series of cases are the following:

Pyelotomy for the removal of small stones in the renal pelvis is an operation with singularly small mortality, and almost a certainty of cure.

Ureterotomy is equally benign. There is a small prospect of relapse, due to stricture of the ureter, which may be minimized by the routine dilatation of the stricture at the point of impaction. But small stones may elude the operator, and large ones call for nephrectomy, the kidney being destroyed.

Nephrotomy is required for the removal of large or multiple stones in the kidney pelvis. Such cases are almost always infected, and though the mortality is not high the trauma to the kidney parenchyma may excite acute focal suppuration, requiring immediate nephrectomy, and may leave the kidney fistulous or severely infected.

Nephrectomy for stone is always a grave operation; but if the opposite kidney is sound and the stones so large or so distributed that they cannot be removed by pyelotomy, nephrectomy is a safer operation than nephrotomy. This immediate safety is, however, balanced in the long run by the loss of the kidney, since stone is likely to form in the remaining kidney.

Stone or infection of the opposite kidney is thus no contra-indication to ureterotomy or pyelotomy; indeed, it is rather an indication for these operations. But it adds immeasurably to the probability of sepsis from nephrotomy and gives a high mortality from sepsis and renal insufficiency following nephrectomy. Hence while we may well continue to operate upon such cases, forced to it by circumstances or moved by the proper surgical ambition to hope for better results by a fuller appreciation of the meaning of renal function tests and by improvement to operative technic, we may do so only under the most favorable circumstances and with a due appreciation that silent renal stone is often compatible with years of life in relative comfort.

EXPERIMENTAL STUDIES IN DIABETES:

SERIES II. THE INTERNAL PANCREATIC FUNCTION IN RELATION
TO BODY MASS AND METABOLISM.

IV. PANCREATIC CACHEXIA.

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NOTICE of the subject of cachexia is necessary in connection with this series of papers, particularly with a view to the possible criticism that undernutrition treatment represents merely a suppression of glycosuria by cachexia, which may mask the diabetic condition without benefiting it. For the sake of unity other aspects of cachexia must be included in the same paper. They add further to the similarity between clinical and experimental diabetes and thus strengthen the application of results gained with the one form to the other. The marked and rapidly fatal cachexia of totally depancreatized dogs, and their deficiency of wound-healing power and liability to infection, have been known from the time of Minkowski. Attention was previously given¹ to Hedon's "diabetes without glycosuria" and to cachectic disorders in partially depancreatized dogs with or without glycosuria. The present observations will be discussed under the following headings:

Acute deaths following operation.

Subacute and chronic pancreatic intoxication.

Diabetic asthenia.

"Gangrene."

Collapse and prostration as related to glycosuria.

Prolonged cachexia.

ACUTE DEATHS FOLLOWING OPERATION.

Deaths from infection occur sometimes, evidently due in part to diabetic lowering of resistance. Clean surgery prevents peritonitis even after total pancreatectomy, until after some days pus may burrow through all the suture lines. Young diabetic animals are as subject to distemper as human patients to tuberculosis.

The highest non-infectious mortality occurs in senile, obese dogs, generally within one to three days after operation, with an extreme and progressive prostration, generally without glycosuria or acidosis. Dogs in advanced senility without obesity ordinarily pass through

¹ Allen, F. M.: Studies Concerning Glycosuria and Diabetes, 1913, chapter x.

such operations safely. Likewise young obese dogs generally survive the operation easily, though when the obesity is extreme and there is much trauma of the pancreas remnant death may occur from the so-called "fat necrosis." At corresponding intervals after operation, examination of the animals which survive with those which succumb shows no perceptible difference in the changes either in and about the pancreas remnant or in the fat elsewhere. It can only be supposed that senility lowers the resistance to the toxic action of the pancreatic juice.

Pregnant animals, regardless of their nutritive state, are known to be highly susceptible to pancreas operations, which are generally followed by abortion and death within one to several days, though various other abdominal operations may be borne safely. As the fatal result is sometimes so early, it is difficult to ascribe it always to septicemia or other secondary consequences of the abortion, and a special susceptibility of the pregnant animal to pancreatic poisoning seems probable.

Prophylaxis of the fatalities in both obese and pregnant dogs has been attempted by two methods, namely, by preliminary intraperitoneal injections of watery extract of dog pancreas and by preparatory removal of small portions of pancreas. The benefit of either method was doubtful. A very old and fat dog sometimes dies from the quick removal of a small fraction of the pancreas. During the period of injections or successive operations the animal sometimes loses considerable weight, and a diminished susceptibility may be thus explainable. A few successful results were obtained with preparation by either method, but a few were also obtained without preparation.

The above statements are based upon a large series of observations, most of which are included in preceding or subsequent papers. For the sake of brevity it has seemed best to omit individual protocols in this place.

SUBACUTE AND CHRONIC PANCREATIC INTOXICATION.

After the usual partial pancreatectomy, which leaves a remnant communicating with its duct, dogs are sometimes more or less depressed and unwell for several days, and lose weight rapidly, partly on account of indigestion and diarrhea. Swelling and inflammation are generally evident in the pancreas remnant during this period. Still greater decline of weight and strength are commonly found when a portion of pancreas is left isolated from its duct, either in the peritoneal cavity or under the skin. The disturbances are generally transitory, continuing a few days or weeks according to circumstances. They are evidently due to toxic products of pancreatic tissue which is inflamed or undergoing absorption. The early wasting and other symptoms are therefore not attributable

entirely to the diabetes, and care should be used in the interpretation of any metabolic observations during this period. Later under suitable conditions the animals are able to digest reasonably well, gain weight and behave normally except for their diabetic tendency, and then are reliable test objects for metabolic study.

DIABETIC ASTHENIA.

If a totally depancreatized, a partially depancreatized and a phlorizinized dog lose equal quantities of sugar in a given time, the totally depancreatized animal will ordinarily show weakness and depression out of all proportion to the other two, and will die while the others are still strong. Even if the totally depancreatized animal appears lively a test with running reveals his lack of strength. The asthenia of partially depancreatized dogs generally appears late in the period of advanced emaciation. Exceptional partially depancreatized animals show early asthenia and rapid progress to death; almost equal to the consequences of total pancreatectomy. These results seem to be classifiable under three headings: (a) Small size of remnant; (b) inflammation in remnant; (c) unknown causes.

(a) Small size of remnant.

Occasional dogs with very small pancreas remnants are strong and long-lived. An example previously published² was dog 19, which had only about one-fifty-fourth of the pancreas, and died in an operation two and a half months later, having been very vigorous for a severely diabetic animal in the meantime. As a rule, animals with very small remnants suffer not only from poor digestion but also from a more rapid decline than can be accounted for by indigestion. Some instances of exceptionally rapid decline are the following:

Dog B2-64.

Male, bulldog mongrel; brindle; age five or six years; medium flesh; weight, 14.7 kilos. May 25, 1914, removal of pancreatic tissue weighing 26.5 gm. Remnant about main duct estimated at 1.35 gm. ($\frac{1}{20}$ to $\frac{1}{21}$). Glycosuria was checked by intermittent fasting and meat feeding, so as to be absent part of the time and never above 1 per cent. (2.6 to 12.8 gm. daily output). Nevertheless, the asthenia was out of proportion to the loss of weight, and exceeded that of other fasting partially depancreatized diabetic dogs. June 15, at a weight of 9.6 kilos, 0.2 gm. of pancreatic tissue was removed for examination. June 20 the dog was sacrificed when moribund. The pancreas remnant weighed 1.1 gm., and the autopsy otherwise was negative. Microscopically, the tissue on June 15

² (Ibid.), pp. 480, 962.

was normal except for marked vacuolation of islands, while that on June 20 showed recent inflammation in addition.

Though life was not extremely short, the noticeable feature was the disproportionate cachexia in comparison with the glycosuria.

Dog D4-75.

Male; bull terrier mongrel; brindle, aged four or five years; slightly thin; weight, 13 kilos. January 19, 1917, removal of pancreatic tissue weighing 35.3 gm. Remnant about main duct estimated at 2 gm. ($\frac{1}{18}$ to $\frac{1}{19}$). The rapidity of decline and the deficiency of healing of the abdominal wound resembled total pancreatectomy. On January 26 the dog was very weak and was killed. The general autopsy was negative grossly and microscopically. The pancreas remnant was swollen and weighed 5.9 gm. Microscopically there was extreme inflammation; the acini stained irregularly and were in various stages of involution and repair; islands were scarce and small and showed early vacuolation.

In this animal the two factors, small size and inflammation of remnant, were evidently combined.

Cats are more subject than dogs to this form of cachexia. They become diabetic with remnants between one-fourth and one-fifth of the pancreas, and when the remnant is much smaller there is cachexia resembling that of total pancreatectomy.

CAT A1-80.

Female; maltese; young adult; slightly thin; weight, $2\frac{3}{4}$ kilos. November 13, 1913, removal of pancreatic tissue weighing 5.4 gm. Remnant about main duct estimated at 0.4 gm. ($\frac{1}{14}$ to $\frac{1}{15}$). The animal showed characteristic depression, weakness and poor wound healing, without peritoneal infection, and refused all food. The urine record was as follows:

Date.	Volume, c.c.	Glucose, per cent.
November 13	60	0
14	100	2.8
15	90	3.8
16	40	3.3
17	80	6.0
18	80	2.7
19	65	2.8
20	50	2.9
21	35	3.1
22	40	4.0

Death occurred November 22, at a weight of 1800 gm. The urine recorded is that found in the bladder at autopsy. In contrast to the emaciation of trunk and limbs there was a surprising quantity of omental and peritoneal fat. The pancreas remnant was swollen

and hard and weighed 1.5 gm. Microscopically it showed much inflammation and fibrosis, together with the usual diabetic vacuolation of islands. The other viscera were normal grossly and microscopically, except for slight fattiness of the liver and the Armanni vacuolation of renal tubules.

CAT A1-81.

Female; young adult; gray striped; good condition; weight, 3 kilos. November 14, 1913, removal of pancreatic tissue weighing 8.3 gm. Remnant about main duct estimated at 0.4 gm. ($\frac{1}{21}$ to $\frac{1}{22}$). The animal ate about 25 gm. meat on November 16 and 17. Otherwise the clinical course was characterized by refusal of food, profound asthenia and rapid decline, with the following urine record:

Date.	Volume, c.c.	Glucose, per cent.
November 14	20	0
15	75	1.5
16	50	3.6
17	50	7.1
18	80	2.5
19	70	1.6
20	60	0.7

The cat was found dying on the morning of November 21 and was killed. The weight was 2 kilos. The liver was very large and fatty, the other viscera normal. The pancreas remnant, normal in appearance and consistency, weighed 0.6 gm. Microscopically it showed fibrosis, chiefly of interlobular type. The acini were in all stages of fulness, emptiness and involution. Islands were almost impossible to find in a series of eight slides containing four sections each. One definite one was found in the last stages of hydropic exhaustion. The others were apparently reduced to small clumps of alpha cells, the identity of which could sometimes be suspected but not clearly demonstrated amid the inflammation. The process of functional exhaustion was thus exceptionally rapid.

(b) Inflammation in remnant.

Dog E5-12.

Male; Dalmatian; aged three years; good condition; weight, 16.25 kilos. March 23, 1917, removal of pancreatic tissue weighing 40.5 gm. The attempt was made to leave a remnant small enough to permit diabetes, yet extending the whole length of the uncinat process. The remnant left consisted of the duct and bloodvessels, with a narrow band of accompanying parenchyma. The dog showed slight appetite on the first two days, but was not fed. There

was marked and increasing prostration like that following total pancreatectomy, with the following urine record:

Date.	Volume, c.c.	Glucose, per cent.
March 23	370	Slight
24	146	1.7
25	810	2.9
26	470	1.8
27	468	3.8
28	248	3.3
29	328	2.4

The dog was found dying on the morning of March 30. There was intense inflammation of the pancreas remnant and distinct congestion and edema of the hypophysis, otherwise nothing unusual in the autopsy.

DOGS C3-83 AND D4-16.

Dog C3-83 became diabetic after removal of five-sixths of the pancreas on April 20, 1916, and dog D4-16 after removal of $\frac{1}{12}$ of the pancreas on the following July 14. The two animals were used for parallel experiments, involving similar glycosuria and other conditions. The contrast in the strength of the two was striking throughout. Dog D4-16 died August 23 while the other dog was still vigorous. The protocols are not given in detail because nothing could prove that some extraneous factor was not the cause of the difference. The number of such observations furnishes evidence that the peculiarity is not accidental. One noteworthy feature in the present instance is the hypertrophy of the pancreas remnant of Dog D4-16, which was estimated at 4.4 gm. at operation and found to weigh 8.2 gm. at autopsy. It thus weighed actually more than the remnant of dog C3-83, which did not hypertrophy. It consisted of normal appearing acinar tissue without fibrosis, with varying numbers of islands. The digestive power should therefore have been as good as in dog C3-83. On the other hand, other studies indicate that the hypertrophy is an indication of preceding inflammation.

(c) Unknown causes.

Dog E5-26.

Male; Newfoundland; black, aged three years; good condition; weight, 24.1 kilos. April 25, 1917, removal of pancreatic tissue weighing 33.7 gm. Remnant about main duct estimated at 5.7 gm. ($\frac{1}{4}$). Glycosuria was absent until bread was fed on April 27 and thereafter was heavy. The dog maintained good appetite and cheerfulness, and behaved normally except for surprising weakness, such that he could stand or walk only with great effort. On May 6 the diet was changed to 200 gm. suet, which was fed daily until May 14, after which lung was added. The glycosuria rapidly

diminished and was absent after May 11, and strength was regained at a corresponding rate, even on the protein starvation. The animal remained strong thereafter in the aglycosuric condition. Such asthenia in early diabetes and gain of strength on complete fasting are sufficiently familiar in human diabetes, but are rare in dogs. No special cause was found in the later history or autopsy of this animal.

CAT B2-06.

Male; yellow and white; old; very fat; weight, 4.2 kilos. May 12, 1914, removal of pancreatic tissue weighing 8.4 gm. Remnant about main duct estimated at 2.9 gm. ($\frac{1}{4}$). The animal ate well and showed heavy glycosuria on milk and meat feeding. At the same time the weakness was marked and progressive, and death occurred June 1 at a weight of 2.8 kilos. The bladder at autopsy contained 55 c.c. urine, with 1.8 per cent. sugar. Except for the very fatty liver, nothing noteworthy was found in the viscera. The pancreas remnant, normal in appearance and consistency, weighed 1.9 gm. Microscopically there was no inflammation or fibrosis except a trifle at the margins. The acini were normal except for minimal zymogen content, which may explain the small weight of the remnant. Islands were present in fair number but were maximally vacuolated.

Remarks. Asthenia is known as a prominent symptom of diabetes, which occurs in the late stages of diabetes in all patients and animals, along with emaciation and other severe disturbances. It occurs much earlier in some patients, most totally depancreatized dogs and in exceptional partially depancreatized animals. Patients generally regain strength under treatment in proportion to the diet they become able to assimilate, but a few continue to complain of weakness even when free from glycosuria and hyperglycemia on diets which are theoretically adequate. Possible causes of asthenia may be considered as follows:

(a) *Loss of Body Fat.* In patients asthenia may be out of proportion to the state of apparent nutrition, may even be present with obesity, and varies between individuals independently of the body weight. Depancreatized dogs, especially if obese before operation, may die while still rich in fat, and at all stages are weaker than normal dogs with a corresponding degree of emaciation.

(b) *Loss of Sugar or Nitrogen, or Both.* The above experiments did not include nitrogen analyses, but there is little doubt that phlorizinized dogs, unless they happen to die from acidosis, may far surpass totally depancreatized dogs in strength and in duration of life, while losing even greater quantities of both glucose and nitrogen. Patients sometimes exhibit asthenia when their carbohydrate and nitrogen balance are still fairly favorable, and the great majority

of them gain strength under fasting and reduced diet³ even though they lose sugar and nitrogen during the process.

(c) *Severity of Diabetes.* If the severity of diabetes be judged by the D:N ratio and respiratory quotient, it is known that totally depancreatized dogs do not necessarily exhibit the maximal ratio, especially during fasting; also partially depancreatized dogs in the later stages of their diabetes may show maximal ratios (and presumably corresponding respiratory quotients) while retaining greater strength and liveliness and living much longer than totally depancreatized animals. If severity be judged by lack of island tissue, a resemblance exists between animals which have had the pancreas completely removed, or in which the remnant is of minimal size or damaged by inflammation, or in which all the beta cells have been lost by hydropic degeneration, as in some of the examples given above. But many animals retain fair strength and live for a number of weeks or months after their beta cells are thus lost, while many patients and occasional animals (*cf.* dog E5-26 above) exhibit marked asthenia while the diabetes is still early and mild. In human cases the asthenia is not even a sign of intrinsic severity, for it is complained of in many cases which are benign and easily controllable throughout. Cases with asthenia out of proportion to the apparent nutrition after cessation of glycosuria are generally grave, but not more so than many others in which the strength is longer retained.

(d) *Nervous Influence.* A neurotic element may be assumed in many patients, whose nervous systems are specially susceptible to the depression of diabetes. Some differences in this respect may be supposed to exist also between animals, but a more important cause is indicated by the fact that in them the asthenia so often progresses to early death.

(e) *Indigestion.* Totally depancreatized dogs and those with very small remnants naturally suffer from impaired digestion and diarrhea. Whether the cause be purely an enzymatic or partly an endocrine deficiency, pancreas feeding in numerous trials in this series has never been able to restore anything like normal digestion. But the differences in strength are found also in fasting animals, and the asthenia of human patients seldom has any relation to digestion.

(f) *Intoxication.* In some animals absorption of pancreatic poisons may play a part, but this is obviously not the case after total pancreatectomy, and it is seldom to be suspected as a cause of the asthenia of human patients. Acidosis is accompanied by a similar and very profound weakness in both patients and animals, but this factor was excluded in the animal experiments, and the type of asthenia in question is often found in patients without acidosis.

³ Ergometric tests in patients were made by J. R. Williams, *Arch. Int. Med.*, 1917, xx, 399-408.

Toxemia of intestinal or unknown origin is assumed by some writers in connection with human diabetes, but there is no reason why totally or partially depancreatized dogs, especially if fasting, should suffer from intestinal intoxication, and the assumption of unknown toxins merely cloaks ignorance and confuses the problem unless some proof of their existence is produced.

(g) *Endocrine Deficiency.* Asthenia is a fairly common symptom of endocrine deficiency, even in cases which involve no impairment of nutrition in the ordinary sense. Addison's disease and some hypophyseal disorders are familiar examples. The most probable theory of diabetic asthenia, aside from the part which is explainable by impaired food assimilation, is that it is an effect of the lack of pancreatic hormone either upon the body cells directly or upon other organs of internal secretion. It would thus be easily comprehensible that this effect might differ somewhat with differences of individual constitution.

"GANGRENE."

A similarity has long been recognized between the gangrene of human cases and the deficiency of wound-healing in totally depancreatized dogs. The dry gangrene which is the commonest clinical form arises always on a basis of arteriosclerosis, and as dogs seem to be not subject to arteriosclerosis, they do not exhibit this form of gangrene. The other form of so-called gangrene, consisting in superficial infections and ulcers which spread instead of healing, occurs in only a small minority of either dogs or patients, and about as frequently in one as in the other. Mention was made in Series I⁴ of dog B2-56, which showed unusually rapid downward progress and cachexia. With this there was a development of trophic ulcers as marked as in any human case. One of these perforated into the right elbow-joint and gave rise to a large abscess in the axilla. Other examples are the following:

Dog B2-11.

Female; mongrel; black and white, aged two years; good condition; weight, 6 kilos. November 20, 1913, removal of pancreatic tissue weighing 16.9 gm. Remnant about main duct estimated at 0.6 gm. ($\frac{1}{2}$). Though the remnant was small and the feces accordingly somewhat bulky, the dog showed no more than the usual glycosuria and other symptoms on meat diet. Early in December something caused a trivial abrasion of the right ankle-joint. By December 8 the whole leg was hot and swollen, without any definite sinus leading from the point of abrasion. Incisions released considerable pus but did not stop the spread of the infection. Death occurred with pneumonia December 11, at a weight of 3 kilos.

⁴ Jour. Exp. Med., 1920, xxxi, 560 and 594.

Dog B2-46.

Male; mongrel; yellow, aged four years; thin but strong; weight, 23.25 kilos. March 26, 1914, removal of pancreatic tissue weighing 32.5 gm. Remnant about main duct estimated at 5.9 gm. ($\frac{1}{6}$ to $\frac{1}{4}$). Glycosuria remained absent until bread feeding was begun on March 30, and was heavy thereafter (up to 6 per cent. in above 2000 c.c. of urine). The asthenia was more marked than in any of the dogs mentioned above as examples of asthenia, and the susceptibility to "trophic" or progressive ulceration equalled or exceeded that of human cases. Death occurred by hemorrhage on April 13.

Other examples will be omitted for the sake of brevity. Certain facts are available concerning the cause of the abnormal liability to infection and necrosis: (1) It is not due to simple malnutrition, for carbuncles and intractable ulcers occur in obese diabetics who are apparently in nutritive equilibrium, and are much commoner among diabetics than among equally undernourished patients with other diseases; (2) it is known that control of the glycosuria and hyperglycemia is the most important means of preventing or curing these conditions, and for this reason speculation has attributed their cause to direct injury of the excess of sugar by osmotic or other action or to the favoring influence of sugar upon bacterial growth. A previous attempt⁵ failed to produce any of the supposed consequences of sugar excess by long-continued injections of glucose or other sugars. In more recent experiments subcutaneous injections of 0.1 gm. phlorizin daily have been found to keep the blood sugar of totally depancreatized dogs at a low level, but their impaired healing power, resistance to infection and other disorders have not been in the least benefited. Furthermore the immense majority of partially depancreatized dogs exhibit healing and resisting power practically identical with the normal, even when their hyperglycemia and glycosuria exceed those of totally depancreatized dogs in both degree and duration. The mere loss of sugar and nitrogen from the body is evidently not responsible, for totally phlorizinized dogs bear operations reasonably well. The factor of dryness of the tissues is also thus controlled, for some phlorizinized or partially depancreatized dogs evidently undergo greater desiccation than the average totally depancreatized dog. (3) The actual endocrine deficiency, in addition to any of the above factors, must be invoked here as in the case of asthenia. The almost uniform difference between totally and partially depancreatized animals is thus explainable, and the special incidence in individual animals or patients may be accounted for by constitutional variations in resistance and the occurrence of predisposing injuries.

⁵Allen, F. M.: Studies Concerning Glycosuria and Diabetes, 1913, chapter iii.

COLLAPSE AND PROSTRATION AS RELATED TO GLYCOSURIA.

Examples were previously given⁶ of the prevention of glycosuria by weakness or prostration, and numerous others might be added from the present series. Dog D4-76 underwent operation on January 19, 1917, and died January 22 from necrosis of most of the pancreas remnant. Here the diabetes should have approached that of a totally depancreatized animal, but the principal symptom was prevented by intoxication. The instance is mentioned because of the similarity to some human cases of fulminating pancreatitis. In Series I, reference was made to animals in which glycosuria was stopped and the progress of diabetes halted by distemper or other causes of anorexia and emaciation. Such animals sometimes later enjoyed excellent health and a high food tolerance in consequence of their spontaneous undernutrition treatment. When the diabetes has become established in a sufficiently severe form, it cannot be halted by fasting or any other known means. In the writer's experience totally depancreatized dogs as well as the partially depancreatized ones with the severest diabetes ordinarily die after continuous fasting or any intercurrent illness or accident with heavy glycosuria present to the end. In the monograph (1913) already mentioned, references were made to the literature concerning absence of glycosuria in totally depancreatized animals after such extreme procedures as removal of the liver or adrenals, or high section of the spinal cord. Any therapeutic significance of such results can be imagined only on the basis of two fallacies, one the confusion between glycosuria and diabetes and the other the indefensible doctrine of diabetes as a pure overproduction of sugar. If it be believed that an animal is diabetic because it cannot assimilate carbohydrate without the internal secretion of the pancreas, obviously the removal of some other organ cannot restore the lost power. Likewise the cessation of glycosuria in occasional totally depancreatized animals in the last hours of life has no therapeutic significance. The very fact of total absence of the pancreas renders such animals unfit for therapeutic experiments unless it is a question of some extract or other agent which can replace the pancreatic function. The results of the undernutrition treatment of patients and partially depancreatized animals are significant for both theory and practice because it can be shown that they do not represent a mere suppression of glycosuria by cachexia, but accomplish an actual raising or preservation of the power of food assimilation and permit a long or indefinite continuance of life.

⁶ (Ibid.), p. 492.

PROLONGED CACHEXIA.

The following are rare instances in which diabetes seemed to be superseded by some unknown cachectic condition, producing results different from those of simple undernutrition. Cats seem to be more liable than dogs to this abnormality.

CAT A1-91.

Male; gray striped; middle aged; slightly thin; weight 3.1 kilos. January 13, 1914, removal of pancreatic tissue weighing 5.8 gm. Remnant about main duct estimated at 1.8 gm. (about $\frac{1}{4}$). There was glycosuria on milk and meat diet and none on meat alone. The appetite and health seemed excellent. The glycosuria was allowed to continue and increase up to 5 per cent. in 455 c.c. urine on February 6. February 7, at a weight of 3.2 kilos, fasting was begun. The glycosuria immediately fell to traces, rose to a moderate reaction on February 10, then fell and was absent after February 12. February 16, at a weight of 2.6 kilos, feeding was begun with 20 gm. cooked beef-lung, increasing gradually until on February 23, 140 gm. lung and a live mouse were fed. The weight meanwhile had been falling rapidly to 1.8 kilos; the cat retained appetite and appeared well except for remarkable weakness and weariness. Lung, suet and raw pancreas were then fed as abundantly as possible. The digestion seemed rather poor, as indicated by bulky formed feces, but the cachexia was more advanced and progressive than is seen in plain fasting. Death occurred February 26, and no cause could be found at autopsy. The microscopic examination of liver, kidneys, adrenals and thyroid was negative. The pancreas remnant, normal in appearance and consistency, weighed 1.8 gm. It was fully normal microscopically; the acini were well filled with zymogen; islands were abundant and free from vacuolation.

CAT A1-94.

Female, adult; white and black; thin; weight, 2 kilos. January 21, 1914, removal of pancreatic tissue weighing 3.7 gm. Remnant about main duct estimated at 0.8 gm. ($\frac{1}{6}$ to $\frac{1}{8}$). The animal refused food except for a trifle of milk, and the highest glycosuria was 0.5 per cent. in 25 c.c. urine. Death occurred on January 25, with urine sugar-free, at a weight of 1.6 kilos. Autopsy showed no cause. The pancreas remnant weighed 0.6 gm., and was normal in acini and islands.

The history of cat A1-95 was closely similar.

Some atypical results of this character caused the writer formerly⁷ to conclude wrongly that cats are unsuitable for diabetic experiments.

⁷ (Ibid.), p. 502.

CAT A1-96.

Male; gray and white; large, strong adult; excellent condition; weight, 3.4 kilos. February 9, 1914, removal of pancreatic tissue weighing 5.6 gm. Remnant about main duct estimated at 1.4 gm. ($\frac{1}{5}$). Glycosuria was produced at first only by milk. It was present March 1 to 23 on meat diet, then ceased spontaneously. With addition of milk it was present March 30 to April 9. On this date two tiny fragments of pancreas, with an aggregate weight of 0.15 gm., were removed for microscopic study. Then on fasting, glycosuria was absent after April 11. A diet of beef-lung or liver was begun with 50 gm. on April 13, increased rapidly to 300 gm. and then *ad libitum*. The cat meanwhile rapidly lost weight and strength without glycosuria, and died April 26, at a weight of 1.9 kilos. The autopsy revealed no gross or microscopic cause of the condition. The pancreas remnant weighed 2.25 gm. Microscopically the tissue removed April 9 was normal except for marked vacuolation of islands. At autopsy there was some interlobular fibrosis; the acini were nearly empty but otherwise normal; islands were scarce in some sections, abundant in others, with most of their cells normal but a few showing slight persisting vacuolation.

In several dogs glycosuria has been unexpectedly absent or has ceased for unknown cause after it has been present for a longer or shorter time. These instances of cachexia have confirmed the previous conclusions⁸ that the duration of life is generally far shorter than in cases in which diabetes develops in typical form. The most marked example of prolonged cachexia was the following:

DOG D4-70.

Male; mongrel; white and black; shaggy; aged four years; medium nutrition; weight, 15.5 kilos. January 10, 1917, removal of pancreatic tissue weighing 31.6 gm. Remnant about main duct estimated at 2.6 gm. (about $\frac{1}{13}$). There was no glycosuria until bread and milk was fed on January 13, causing a slight reaction which disappeared on the same diet. Beginning January 18 a diet of bread and 200 gm. glucose maintained glycosuria until January 23, when it ceased. Thereafter the dog ate the same full pan of bread, with 300 gm. glucose, 200 gm. lung and 100 gm. suet without glycosuria. Beginning January 27, analyses of urine and feces were performed on a diet of 200 gm. lung, 250 gm. bread and 100 gm. suet, which showed only a moderate deficiency of food absorption; also a genuinely high tolerance was demonstrated by an intravenous glucose test and a series of blood sugar analyses, but all these records were lost. February 10, 0.5 gm. phlorizin suspended in oil was

⁸ (Ibid.), p. 500.

injected subcutaneously, and heavy glycosuria continued until February 15, indicating a full ability to form and excrete sugar under this stimulus. The weight had mostly remained low, between 13 and 14 kilos, but rose by April 4 to 16.4 kilos. At this weight the feeding of bread and soup *ad libitum* with 100 gm. glucose brought on glycosuria, which ceased promptly when the diet was changed to 400 gm. lung and 200 gm. suet. By May 4 the dog was still lively and happy, with enormous appetite, but was showing hair loss and unsteadiness of legs. Because the symptoms resembled those of fat intoxication (produced in normal dogs by diets too high in fat and low in protein) the diet was changed on May 22 to lung and bread, with milk occasionally, and bonemeal to supply salts. On June 12 and July 27 small portions of pancreas were removed for



microscopic examination without giving rise to glycosuria. The pancreas remnant appeared normal grossly and microscopically. The body weight fell as low as 10.3 kilos, notwithstanding edema, but rose later to 12.5 kilos. Death occurred, apparently from simple weakness, on September 27. The pancreas remnant, slightly firm and nodular, was in free communication with its duct, and weighed 2.9 gm. Microscopically it showed slight fibrosis, interacinar as well as interlobular, but the acini were large and well filled and the islands abundant and normal. Gross and microscopic examination of the other viscera revealed no abnormalities to account for the condition.

The above photograph was taken on July 5. The dog unfortunately was not photographed when normal, but was a rather

handsome animal with long thick hair. The hair loss is seen on the head and ears, trunk, limbs, and the naked end of the tail visible between the legs. Edema without evidences of nephritis is occasionally seen in cachectic dogs, even without pancreas operations. It was greater here in the hind than in the front limbs, and was not like myxedema, but consisted in an accumulation of clear fluid which flowed freely from a needle puncture. The dog remained in excellent spirits throughout. Signs of sexual activity were completely lacking, and the animal was somewhat silly in mentality, as J. H. Pratt has stated⁹ concerning young dogs with pancreatic atrophy.

Conclusions. 1. In addition to some acute deaths from unknown causes shortly after partial pancreatectomy, examples were given of diabetic asthenia and diabetic gangrene in animals, which add another detail to the resemblance between clinical and experimental diabetes. Reasons were given for considering both the asthenia and the gangrene as due not to simple malnutrition, hyperglycemia, glycosuria or other causes, but rather to the specific endocrine deficiency.

2. Examples were also given in which the diabetes of dogs and cats was replaced by a fatal cachexia of unknown nature. It is not certain that the condition in all these instances was the same. Malnutrition due to impaired digestion or intestinal absorption was probably one factor, but the results seem to differ in some respects from simple undernutrition, and may possibly bear some relation to the metabolic alterations in states of prostration which suppress glycosuria even after total pancreatectomy.

3. It is highly important to distinguish the mere suppression of glycosuria by some injury, poison or cachexia from genuine control or improvement of the diabetes. It is thus impossible to use totally depancreatized dogs for any therapeutic experiments, unless for testing some agency which is supposed to replace the internal pancreatic function. The results of the undernutrition treatment of animals and patients are distinguished from mere cachectic suppression of glycosuria by the fact that the power of food assimilation is demonstrably strengthened, the general health improved and life lengthened instead of shortened.

⁹ Personal communication. Also Jour. Am. Med. Assn., 1912, lix, 322-325.

PULMONARY SEQUELS OF INFLUENZA.

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THE vast majority of patients affected with acute epidemic influenza recover and hardly any traces are left behind, as far as can be ascertained by available clinical methods. In a small proportion, after the acute symptoms have subsided, the patients remain with certain pathological changes in the respiratory tract, producing annoying symptoms often confusing to those who attempt to ascertain the real trouble. These chronic symptoms, as well as the pulmonary lesions responsible for them, last for months in many cases, while in some the pathological changes in the lungs and bronchi appear to be so serious that a *restitutio ad integrum* can hardly be expected. During the past two years the number of patients presenting symptoms and signs of chronic disease of the respiratory organs directly traceable to acute epidemic influenza has been quite large. It is the purpose of this paper to offer a brief outline of the pathology, symptomatology, and prognosis of the sequels of influenza in the respiratory tract as encountered by the writer in private and hospital practice.

Chronic influenza was already noted by clinicians after the epidemic of 1890-1891. Thus, R. Pfeiffer¹ speaks of chronic influenzal bronchitis lasting several months after the acute disease had run its course. The symptomatology and course of the trouble as described by Pfeiffer does not materially differ from those recently observed by the writer in New York. Similarly, Finkler,² Albert Fraenkel,³ J. Tessier,⁴ Maizon,⁵ Collet and Chotin,⁶ Egger,⁷ and many others, have some twenty-five years ago described in detail certain forms of chronic influenza, and many have emphasized that its differentiation from pulmonary tuberculosis is often very difficult.

Since the epidemic of the past two years several writers in Europe have also described chronic forms of influenza. S. Korach⁸ F. Meyer,⁹ Ch. Roubier,¹⁰ Feilchenfeld¹¹ and others have either men-

¹ Die Aetiologie d. Influenza, Ztschr. f. Hyg. u. Inf., 1893, xiii, 357.

² Infektion d. Lungen durch Streptokokken u. Influenzabazillen, Bonn, 1895.

³ Mitt. über influenza, Deutsch. med. Wchnschr., 1894, xx, 49; Spez. Pathol. u. Therap. d. Lungenkrank., Berlin, 1904, pp. 436, 530, 534.

⁴ Leçons sur la grippe-influenza, Paris, 1893.

⁵ De la grippe chronique a forme tuberculeuse, Thèse de Lille, 1894.

⁶ Deux cas de grippe a forme pseudo-phymique, Lyon médicale, 1894.

⁷ Etude clinique des formes pseudo-phymique de la grippe, Thèse de Lyon, 1894-1895.

⁸ Zur Pathologie d. Influenza, Berl. klin. Wchnschr., 1919, lvi, 218.

⁹ Zur Behandlung d. Grippenpneumonie, Deutsch. med. Wchnschr., 1919, xlv, 173.

¹⁰ Grippe et tuberculose, Lyon méd., 1919, li, 428, 485.

¹¹ Aus d. Aerztlichen Praxis, Deutsch. med. Wchnschr., 1919, xlv, 439.

tioned it or given complete descriptions of the various clinical forms in which these chronic sequels manifest themselves. J. E. Kayser-Petersen¹² describes tracheobronchial adenitis, at times reactivation of old tuberculous lesions in these glands, as sequels of influenza. Fürbinger¹³ speaks of chronic pneumonia without tubercle bacilli in the sputum as frequent sequels. Fraenkel and Krehl¹⁴ emphasize the above views and state that in many cases only repeated examinations of the sputum decides the diagnosis. O. Bossert and B. Leichtentritt,¹⁵ have described chronic pneumonic processes in children as sequels to influenza. Brüggemann¹⁶ gives details of chronic perichondritis of the larynx following epidemic influenza, which is very difficult to differentiate from syphilis and tuberculosis of the throat.

As encountered in the practice of the writer the chronic forms of influenza manifest themselves in various clinical pictures. In a large proportion of cases, especially those in which the primary disease ran a moderately mild course without pulmonary complications, the lesion in the throat lingered on for weeks or even months. In others in whom the bronchi were severely affected during the course of influenza, subacute, purulent bronchitis, general or apical, remained for an indefinite time. In still others in whom the lungs and pleura were implicated during the course of the primary acute disease, bronchiectasis, chronic abscess of the lung, thickened pleura, etc., remained. Many of these patients were pronounced tuberculous and admitted to sanatoriums and hospitals for tuberculous.

Rhinopharyngitis. In a considerable proportion of patients who recover from the acute symptoms of influenza the persisting cough and expectoration are due to a lingering or chronic inflammatory process in the pharynx and tonsils. In some the redness of the fauces remains for weeks and months and they persist in hawking, coughing and expectorating; they remain weak and debilitated; some are completely disabled from pursuing their vocations. Rarely hoarseness is a pronounced symptom, but perichondritis of the larynx, as described by Brüggemann,¹⁶ has not been observed by the writer. Fever is entirely absent in most cases, though instability of the pulse-rate is to be observed. Bradycardia, however, is not rare. In a few slight exertion was instrumental in raising the temperature. Owing to their debility, lack of endurance and cough, they are treated either for neurasthenia or as tuberculosis "suspects." Physical exploration of the chest fails to reveal anything abnormal in the bronchi and lungs. In those in whom certain

¹² München. med. Wchnschr., 1919, lvi, 1261.

¹³ Quoted from Petersen, *Ibid.*

¹⁴ *Ibid.*

¹⁵ Chronische Lungenkrankungen bei Kindern infolge Influenza, Deutsch. med. Wchnschr., 1919, vol. xlv.

¹⁶ Perichondritis des Kehlkopfes nach Grippe, München. med. Wchnschr., 1919, lvi, 641.

abnormal findings are elicited by physical exploration of the chest, due in fact to preëxisting disease of the pleura or lung, and which are ordinarily disregarded by careful physicians, a diagnosis of tuberculosis is liable to be made. Several of these cases have been referred to the Montefiore Hospital as tuberculous:

CASE I.—I. C., admitted July 20, 1919. An errand boy, aged nineteen years; his father died of pulmonary tuberculosis and he had an attack of pneumonia five years previously. He recovered and felt well until January, 1919, when he was laid up with influenza for a week. He then resumed work, but weakness and debility prevented and he applied to the Department of Health for diagnosis and treatment. He was sent to the Municipal Sanatorium for the Tuberculous and then transferred to another hospital for advanced tuberculosis. Neither institution suited his fancy and he asked to be transferred to the Montefiore Hospital.

On admission he complained of cardiac palpitation, weakness, dyspnea on slight exertion, pains in the chest and loss of weight. A careful physical examination showed no abnormal findings in the lungs and bronchi, excepting some slight impairment of resonance over the right apex. The breath sounds were normal and no adventitious sounds could be elicited. A radiogram of the chest did not show anything abnormal. While at the hospital his temperature, pulse and respiration were normal; the urine was negative. No sputum could be obtained for examination because he did not expectorate, nor did he cough. His fauces showed the characteristic signs of inflammation.

CASE II.—F. M., woman, aged thirty-eight years. Family and personal history irrelevant, excepting that in 1912 she "caught cold" and coughed. Physicians diagnosed bronchitis at the time and she was relieved by medication. She felt well until October, 1918, when she contracted influenza and again began to cough. After remaining in bed for about two weeks the fever, etc., disappeared, but she continued to cough, expectorate, felt rather weak and lacked endurance. But her pulse, temperature and respiration remained normal throughout her stay at the hospital. Repeated examinations of the sputum failed to disclose tubercle bacilli, though various cocci were found. On physical examination nothing abnormal could be discovered in the chest outside of slight impairment of resonance over the right apex. The redness of the fauces has been marked. For about nine months, weakness, cough and expectoration have persisted.

These two cases illustrate the rhinopharyngeal form of chronic influenza. We have met with numerous cases of this type during the past two years. It has been our experience that the prognosis

is very good. Sooner or later, in some cases after six to twelve months, strength is regained concurrent with the disappearance of the local inflammatory phenomena in the throat. A rest out of town for a few weeks is perhaps the best mode of treatment.

Purulent Bronchitis of Influenzal Origin. Of greater significance is a persisting inflammatory process in the bronchi with resulting purulent bronchitis, of which we have seen many cases during the past two years. More or less severe cough, profuse expectoration of mucopurulent, rarely purely purulent material, teeming with cocci or influenza bacilli, and debility persist for weeks, at times for months. It is noteworthy, and of diagnostic significance, that despite the extensive catarrh of the bronchi most of these patients have no fever; and the pulse may be normal, at times even bradycardia is observed, and they do not lose in weight; many even gain in weight to a remarkable extent. In several cases I have observed dyspnea on slight exertion, in a few acrocyanosis.

Physical exploration of the chest shows that its resonance remains unimpaired and there are no changes in the breath and voice sounds, but that adventitious sounds of various kinds abound all over the chest, or at least over the lower lobes of the lungs posteriorly. The diagnosis is clear and no suspicion should be entertained that we are dealing with a more serious condition than catarrhal bronchitis. It will be observed that, despite the cough and profuse expectoration of purulent or mucopurulent material, the general condition of the patient hardly suffers; in fact, he may be gaining in weight and may also be able to pursue his occupation, though more or less annoyed by the symptoms. It has been my impression that diffuse purulent bronchitis is more liable to occur in patients who during the attack of influenza had symptoms of general bronchitis; those suffering from complicating bronchopneumonia are left, as a rule, with symptoms and signs of localized bronchitis or bronchiectasis, as will be shown later on. In several cases in which myocarditis was one of the sequels of acute influenza there was found, in addition to the dyspnea, acrocyanosis, tachycardia, etc., a dry form of bronchitis with sibilant and sonorous rales all over the chest.

The diagnosis is arrived at by the method of exclusion. Diffuse purulent bronchitis is usually secondary to cardiac or renal disease, both of which are lacking in the influenzal cases. The fact that the symptoms have appeared with occurrence of acute epidemic influenza, have persisted after the acute attack subsided, that there is no serious effect to be observed on the general nutrition of the patient, and that despite its abundance the sputum lacks tubercle bacilli, should all be considered. The prognosis is good, though in some cases the symptoms are liable to linger for weeks and months. I have cases under my care in which the cough and expectoration have lasted over a year. A short vacation in the country appears to be the best and most effective mode of treatment. Expectorant medi-

cation has no effect on the local lesion, nor on the annoying symptoms; while it is liable to cause gastric derangement.

Apical Catarrh. Some twenty years ago several authors spoke of apical catarrh of influenzal origin, but others maintained that it is almost invariably tuberculous in character. However, during the past two years the number of patients with catarrhal lesions in the upper lobes of the lungs without tubercle bacilli in the sputum has increased enormously. Many of them are being treated as tuberculous; nearly all give a history of epidemic influenza at the onset.

The differentiation between influenzal apical bronchitis and pulmonary tuberculosis is at times very difficult indeed. The writer has been guided by the following points: Its onset with influenza speaks against tuberculosis. The lack of constitutional symptoms of phthisis, especially fever, tachycardia and emaciation, is greatly against tuberculosis, because active phthisis with numerous rales audible over an apex, a slow pulse-rate and normal temperature are exceedingly rare, excepting in far advanced fibroid cases, which are easily diagnosed along other lines. Lack of signs of pulmonary retraction of the affected apex as revealed by topographic percussion, also favors apical catarrh—the resonance above the clavicle remains unimpaired despite the presence of numerous subcrepitant rales and perhaps bronchovesicular breathing; this is hardly ever seen in tuberculous apical lesions. If to these is added the fact that, though abundant, the sputum is negative on several examinations, tuberculosis should be excluded. It may also be added that blood-streaked sputum does not by any means favor the diagnosis of tuberculosis in this class of cases. On the whole it will be noted that these apical sequels of epidemic influenza do not at all impair the general health of the patient. He coughs and expectorates, at times blood-streaked sputum, but he maintains his weight, has a good appetite and gains in weight, although some rales are heard while his chest is auscultated.

Bronchiectasis. Bronchiectasis has heretofore been somewhat of a mysterious disease, especially as to its origin. Some authors have considered it very rare while others stated that they meet with many cases; some said that most cases are due to foreign bodies in the bronchi and urged bronchoscopic treatment (Chevalier Jackson). Many writers have maintained that bronchiectasis originates mostly in influenza. Pfeiffer pointed out that the contents of bronchiectatic cavities are often teeming with influenza bacilli. Osler¹⁷ agreed with this view. He said: "The disease seems to have increased in frequency since the influenza epidemics of the past fifteen years." The writer, dealing in his hospital work with large numbers of Eastern European patients, has met with numerous cases of bron-

¹⁷ Principles and Practice of Medicine, 1916, 8th ed., p. 625.

chiectasis, the history showing that the disease was acquired long before the patients had emigrated to the United States. Among native patients the number with dilated bronchi was much less. This may explain the reason why there is such a divergence of opinion as to the frequency of bronchiectasis. It apparently depends on the character of the clinical material. However, during the past two years, since the pandemics of influenza, large numbers of patients are met who present symptoms and signs of bronchiectasis and who date the origin of their trouble to the epidemic disease. At present bronchiectasis, if for its frequency alone, assumes greater importance from the standpoint of diagnosis, prognosis and treatment than formerly when cases were comparatively scarce, at least among the native population.

The lesion follows bronchopneumonia, pleurisy or both. Small areas of bronchopneumonia of a chronic type occur and excessive growth of connective tissue is effective in contracting and destroying the pulmonary parenchyma; the elasticity of the lung tissue is thus impaired, and, contracting, the elastic fibers of the air vesicles, are strangled. Atelectasis, on the one hand, and accumulation of secretions in the stenosed bronchial tubes on the other, are effective in producing dilatation of the bronchi. In cases in which pleurisy complicated the acute disease, the productive inflammatory process emanating from the pleura sends forth strands of connective tissue into the parenchyma, and these have the same effect as the process just described. Pathologically the lesion is chronic bronchopneumonia, with resulting bronchiectasis. Douglas Symmers,¹⁸ who has made excellent studies of the pathology of cases of influenza that came to necropsy during the last two pandemics in New York, points out that the residuum of bronchopneumonia after organization and overgrowth of connective tissue, should in patients who survive the acute disease result in the formation of bronchiectasis, an expectoration of pus from bronchial fistulas and the like. He is of the opinion that these lesions occur mainly in patients with pleural involvement.

In the vast majority of cases the diagnosis offers no difficulty because the lesion is localized in one of the lower lobes of the lungs. The patient gives a history of an acute disease which was diagnosed as influenza; he also says that the acute disease was complicated by bronchopneumonia or pleurisy, or both. The fever abated by lysis, but now and then he again suffers from hyperthermia for several days. The cough has not ceased, however, and the expectoration has been profuse some days, while during others it has been scanty or altogether wanting. If the disease has lasted for several months the cough and expectoration may be influenced

¹⁸ Difference in Pathology of Pandemic and Recurrent Forms of So-called Influenza, Jour. Am. Med. Assn., 1920, lxxiv, 646.

by posture. While lying down on one side or sitting up in bed, or on reclining, a fit of coughing is brought on. If large doses of anodyne medication are administered with a view of controlling the cough during the night, the patient has miserable morning hours while the accumulated secretions are being expelled from the chest soon after rising. These patients may be trained to empty the cavities in the chest several times a day, thus acquiring comparative rest and comfort in the intervals.

Hemoptysis is not rare. Usually the amount of blood expectorated is slight, only streaks are noted, but this is sufficient to unduly alarm the patient, and at times his medical adviser. Many cases of more or less copious pulmonary hemorrhage have been seen by the writer among this type of bronchiectatics. The symptoms during the bleeding are not unlike those seen in phthisis, and at times it is very difficult to differentiate these conditions at the first examination of the patient.

While in most cases the course of the fever is undulating, we have met with cases in which the curve was continuous or remittent, as in progressive pulmonary tuberculosis. During the afternoon the fever rises to 100° or 101° F., rarely higher. Others are met with in which the temperature is normal for days or weeks, when suddenly it rises, producing the common constitutional symptoms of fever (Case III). These acute exacerbations are usually concurrent with a lessening of the amount of sputum brought up by the patient, and with the recurrence of drainage of the cavities manifesting itself by copious expectoration of sputum the fever subsides.

During these febrile exacerbations the pains in the chest, usually felt over the affected area, may be intensified. In some cases the pain in the chest is reflected to the abdominal wall or the shoulder of the affected side. This is the case especially when there are adhesions of the diaphragmatic pleuræ.

Dyspnea, subjective or objective, is often a prominent symptom. It is usually due to toxic myocarditis. After the disease has lasted for some time, dyspnea may be caused by pulmonary fibrosis, interference with the lesser circulation, resulting in dilatation of the right heart, and, at times, by cardiac displacement, especially in left-sided lesions in which the pleura has been implicated. The pulse-rate is normal in many instances, but in some tachycardia, cardiac palpitation and precordial distress are prominent symptoms, especially in those in whom toxic myocarditis is pronounced. Acrocyanosis and sweating of the hands have often been observed.

Because they simulate pulmonary tuberculosis, and the traditional notion that influenza is a strong predisposing factor of tuberculosis, these patients are often erroneously diagnosticated and referred to sanatoriums. However, mistakes are easily avoided when the following points are borne in mind: It is exceedingly rare that tuberculosis should follow influenza, as was shown by the

writer elsewhere.¹⁹ The fact that the patient had not coughed before the onset of influenza speaks against tuberculosis even when there are symptoms simulating active phthisis. Physical exploration of the chest usually clinches the diagnosis. The lesion is in most cases found in one of the lower lobes of the lung, usually the left. The resonance is impaired over one base and the breath-sounds are feeble or even absent. Cavernous breath sounds, which are mentioned in many text-books as frequently found in bronchiectasis, have hardly ever been heard by the writer in this class of cases. The most characteristic sign is the presence of coarse, moist rales audible over a circumscribed area of the chest. Cough may provoke these rales in those in whom they are not audible during ordinary or forced breathing. In cases in which the lesion is thus localized in one of the lower lobes the diagnosis is simple. Tuberculosis in which the lesion is confined to a lower lobe, while the apices remain free from pathologic changes, is extremely rare and may be left out of consideration in everyday practice. The fact that, despite its abundance, the sputum is negative as regards tubercle bacilli is confirmatory. In addition, it is noted that with an extensive pulmonary lesion involving one entire lower lobe the patient is not much if at all emaciated. The facies of phthisis is lacking and instead we find cyanosis of the lips and finger-nails. Clubbed fingers are very common.

The following cases have been selected from among many because each illustrates certain points in the diagnosis and course of these pulmonary lesions:

CASE III.—M. L., bookkeeper, aged thirty-three years. Had been under the writer's care for minor ailment for several years, and for this reason his lungs and bronchi are known to have been free from any gross pathological changes, until an attack of influenza and complicating bronchopneumonia during October, 1918. The pneumonia was rather severe, but he was on his way to recovery within three weeks after the onset, the temperature dropping by lysis. He continued coughing ever since, and expectorates large quantities of mucopurulent material. He has pain in the lower part of the left side of the chest. His temperature is normal for a week or two, when, without any discernible cause, though he believes that after "catching cold" it rises to 101° F. or even higher, it remains at that level for a few days or a week and then drops again to normal. He can only sleep on the right side with comfort; as soon as he turns on the left side he is liable to provoke a violent fit of cough and expectoration. At times the sputum is streaked with blood. Repeated microscopic examinations of the sputum failed to reveal tubercle bacilli. Various cocci, especially diplococci, are,

¹⁹ Fishberg: Influenza and Tuberculosis, Am. Rev. Tuberc., 1919, iii, 532.

however, found in every smear. Of late he suffers from dyspnea on slight exertion. His lips and fingers are slightly cyanosed, and evidences of clubbing of the fingers have made their appearance. Now and then he suffers from attacks of emetic cough,—after a fit of coughing vomiting is provoked and this gives him relief. His general nutrition has suffered but little. During the febrile periods he loses five or six pounds in weight, but he soon regains it and even more during the afebrile periods. The physical signs show a catarrhal lesion in the lower lobe of the left lung: Impaired resonance, feeble breath-sounds and coarse, moist, consonating rales are audible over that area. There are signs of slight displacement of the heart to the left; the diaphragm is drawn upward.

CASE IV.—M. S., aged thirty-nine years. Past and personal history have no bearings on his present trouble. Seven months before admission to the Montefiore Hospital he sustained an attack of influenza complicated by bronchopneumonia. Ever since the fever subsided by lysis he has kept on coughing, expectorating and has had pains in the chest. Especially annoying to him has been a sense of weakness and aching of the limbs on slight exertion. He states that since he has been out of bed he has had no fever but now and then he has noted some night-sweats. At the clinic of the Department of Health he was pronounced tuberculous in the advanced stages of the disease and referred to this hospital. Physical examination on admission showed a fairly healthy looking man, excepting that his lips and finger tips are slightly cyanosed. The resonance over the chest was found defective above the second rib anteriorly on the left side and over both bases posteriorly. Over the left apex cavernous breath sounds were audible; over both bases feeble breath sounds. Medium sized, moist rales were heard posteriorly on both sides over the bases of the lungs; after coughing some moist rales could be provoked over the left apex.

Throughout his stay at the hospital for six weeks we found his pulse-rate, temperature and respiration normal; blood-pressure 120 systolic and 80 diastolic; urine negative. A slight leukocytosis with an increased proportion of the polynuclear cells was found. A laryngological examination proves negative; only slight deviation of the septum was noted by the rhinologist. Repeated examinations of the sputum, ordinary smear preparations and with anti-formin, proves negative as regards tubercle bacilli.

This patient was discharged as non-tuberculous because of the discordance between the findings on physical exploration of the chest and the constitutional symptoms. If the lung lesions disclosed by the physical signs were of tuberculous origin the patient would have suffered from fever, tachycardia, emaciation, etc. Tuberculous patients expectorating as freely as this one did, almost invariably

have demonstrable tubercle bacilli in the sputum. Especially is this true of tuberculous lesions in the lower lobes of the lungs. In this case the physical signs showed clearly a lesion in the upper lobe of the left lung in addition to the basal lesions, and for this reason we kept the patient in the hospital for six weeks, repeatedly examining his sputum and observing his pulse, temperature, etc. As in many others, this case confirmed our observation that tuberculosis hardly ever follows influenza;²⁰ the few cases observed by the present writer may be considered coincidental. If the patient is reliable, and we are assured that he never had coughed before the onset of influenza, or, what is even better, if we know from personal observation that before the attack of influenza the upper lobes of the lungs were free from pathological changes, we may safely conclude that the localized lesion is the catarrhal or the bronchiectatic form of chronic influenza. At the Montefiore Hospital experience during the past three years has taught us that lung lesions following acute epidemic influenza, irrespective of the symptoms they produce, and the signs elicited while examining the chest, are not tuberculous. This diagnostic principle has helped us materially.

Observation of a large number of cases of this type has disclosed certain characteristics which differentiate these lesions from tuberculous. In many the impaired resonance elicited over the upper lobe is mainly found below the clavicle while in the supraclavicular fossa an almost normal note is brought out; often a tympanitic overtone is audible. In tuberculosis there is almost invariably pulmonary retraction and narrowing of Krönig's areas. The bronchiectatics never have laryngeal and intestinal complications which are frequent among tuberculous with such extensive lesions. With profuse expectoration, fever, night-sweats, emaciation, etc., are the rule in tuberculous lesions, and hardly ever observed in bronchiectatic. A completely unilateral lesion speaks in favor of bronchiectasis.

Radiography is at times of assistance in differentiating these cases. In tuberculosis the shadow indicating airless tissue is found above the second rib, in addition to any other shadows that may be observed, while in post-influenzal bronchiectasis the lung markings are almost normal in that location. The lesion is discerned on the plate exclusively in one of the lower lobes. Signs of a thick pleura and enlarged bronchial glands are commonly observed. The shadow may appear dense one day, while on another, after the secre-

²⁰ This statement has been questioned by many writers who quote statistics to the effect that a large number of patients admitted to sanatoriums during the past three years state that they have had influenza before the symptoms of tuberculosis became manifest. But it must be borne in mind in this connection that about 25 per cent. of the population in this country has been affected with influenza during the several epidemics waves which occurred since 1918. Especially has the proportion been high among persons between fifteen and forty-five years of age, the period of life when active phthisis is most liable to occur. It is thus to be expected that about 25 per cent. of persons who develop phthisis at present should give a history of having had influenza during the epidemics.

tions have been removed by expectoration, it may clear up, though lung marking are still lacking. Even when the upper lobe is affected, which is rare in bronchiectasis, the cough phenomenon shows that there is little, if any, retraction in bronchiectasis; the parenchyma above the clavicle brightens up during cough, while with tuberculous lesions the reverse is true. In many cases in which fibrosis has been active, or the pleura is implicated in the process, there may be noted some visceral displacement—the diaphragm is elevated and the mediastinum is drawn toward the affected side.

The prognosis in these cases appears to be favorable as regards life, but gloomy as regards relief of the symptoms. The writer has cases under his care acquired many years ago, and thus believes himself to be in a position to state that he has not seen one in which the symptoms have disappeared completely. They keep one coughing, expectorating, are more or less dyspneic and cyanosed though they hardly lose in weight—some even gain in this regard. Their life appears to depend on the undulating course of the disease, with ups and downs. That which they consider "catching cold" consists in acute exacerbations of fever, pains in the chest, profuse expectoration, etc. After a few weeks of misery due to these symptoms they again feel better in a measure for an indefinite time, till they again "catch cold" when the acute symptoms return. During these acute exacerbations, pneumonia is frequently diagnosed because the signs elicited over one of the lower lobes, combined with the fever, pain in the side, etc., are not unlike those of some aberrant cases of pneumonia. Patients met by the writer who have had this sort of bronchiectasis for many years give a history of several attacks of "pneumonia." Some live to an advanced age and finally die from pneumonia, exhaustion due to amyloidosis, dilatation of the heart with edema, etc. In rare cases the end comes through complicating gangrene of the lung.

Pulmonary Suppurations.—The most serious sequels of influenza appear to be pulmonary suppurations of which we meet now more than before the pandemic of 1918–1920. They are serious because of the severity of the symptoms, and the gloomy outlook for recovery.

Pulmonary suppurations occur almost invariably in influenzal patients in whom the complicating bronchopneumonia was of a stormy type. In nearly all cases I have elicited the fact that during the acute disease the physician in attendance gave a fatal prognosis, though ultimately recovery of a sort ensued. Nearly all pathologists who reported necropsies on fatal cases of influenza mention that the number with pulmonary and subpleural abscess was large. Douglas Symmers and Morris Dinnerstein¹⁸ found 35.5 per cent. of fatal cases were associated with the presence of intrapulmonic abscess, which varied in size from minute affairs to purulent foci approximating 2 or 3 cm. in diameter. In one case the upper lobe

of the lung was almost completely replaced by multiple or intercommunicating cavities. The writer has seen several of these cases clinically. While most of the patients with pulmonary suppurations succumb to the acute process, some recover, or at least linger along for several weeks or months.

In nearly all cases of pulmonary abscess of influenzal origin the history shows that the patients had not been relieved from the symptoms of pneumonia, but that for weeks after the onset of the acute disease the symptoms of acute intoxication have persisted. The fever remains high, the prostration is marked, and the patient expectorates large quantities of purulent material, at times fetid, often tinged with blood, and containing elastic tissue. In some cases copious pulmonary hemorrhages have occurred. Pain in the affected side of the chest is a prominent symptom. In the comparatively few cases which are not immediately fatal the fever abates several weeks after its onset and the general condition apparently improves more or less, but sooner or later another acute exacerbation occurs and the patient is again laid up with fever, prostration and pain. Such exacerbations and remissions recur at irregular intervals supplying false hopes of recovery one the one hand, or despair on the other. More or less copious pulmonary hemorrhages occur in many cases and after each bleeding the copious expectoration, the pain in the chest, and the fever may be ameliorated. The general condition of the patient, especially his weight and feeling of well-being oscillate, depending on the pulmonary symptoms and the fever. During the acute exacerbations the patient loses ground, but as soon as he becomes afebrile he picks up again and he may thus hold his own for many months; in the pronouncedly chronic cases he may even be the gainer in this regard, especially when the abscess cavity drains freely. The marked emaciation of advanced tuberculosis, which some cases simulate exquisitely, is never seen with chronic pulmonary abscess, nor is there to be seen the hectic facies of phthisis. However, cyanosis of the lips and finger tips, and dyspnea are dominant symptoms in most cases. Clubbing of the finger may occur within a short time.

Physical exploration of the chest is often deceptive soon after the symptoms of the acute infection have passed. The signs are usually those of a pleural effusion in the lower part of the chest. Exploratory puncture, however, proves negative. Within a few weeks it is noted that while the flatness and feeble breath-sounds remain, there appear coarse, moist, consonating rales audible over the affected area; concurrent with the appearance of these rales the patient also begins to expectorate large quantities of purulent material often mixed with blood. While in some cases the fever declines with the onset of copious expectoration, in most it keeps at high level for several weeks. Then the undulating course mentioned

above begins; at some period the patient may be afebrile to be stricken again with fever after a few days or weeks.

The patient then enters the chronic stage of the disease. The lungs all over clear up, no signs of disease are to be found on physical exploration of the chest, excepting over the site of the lesion where dulness, or flatness, feeble breath-sounds and large, moist rales are elicited. In most cases the lesion is in one of the lower lobes; in very few, in one of the upper or the right middle lobe, and several cases in which almost a complete lung was implicated in the suppurative process were seen by the writer. In some cases the odor of the sputum is offensive; it is disagreeable, but it has not the sharp, penetrating, disgusting, or cadaverous odor of pulmonary gangrene. The sputum when collected into a conical glass is seen to separate on standing into three layers, and microscopically elastic fibers are discovered in addition to a variable flora of microorganisms among which Pfeiffer's influenza bacillus is not dominant.

The inflammatory process may reach the pleura and an effusion takes place. But when we have signs of fluid, confirmed by exploratory puncture, we should not forget that there is an underlying suppurative process in the lung and a guarded prognosis should be given. The history will often help in the diagnosis, but the following points may be taken into consideration: In simple pleurisy with effusion the patient coughs, but he brings up little if any sputum, while in cases with abscess considerable quantities are expectorated, at times ill-smelling, or tinged with blood. Rarely copious hemorrhages occur. In several cases under the writer's care the effusion was purulent; in one, sanguineous.

From among many cases observed by the writer during the past two years, the following have been selected as typical:

CASE V.—I. R., woman, aged thirty-two years, born in Italy, married. Father died from cirrhosis of the liver, a brother, from meningitis at the age of two. She has been married thirteen years, has had three children and two miscarriages, one induced.

November, 1918, while seven months pregnant, suffered from an attack of influenza complicated by bronchopneumonia, recovered in three weeks. She, however, did not become completely afebrile, and continue coughing, expectorating large quantities of purulent sputum, remained weak, etc. In January 1919 was delivered of a full term infant, followed by a severe postpartum hemorrhage. The cough then became even more aggravated, chills and fever reappeared and she was removed to a hospital where she was told that she had pneumonia in the left lung. Her symptoms at that time were severe cough, profuse expectoration, hemoptysis, fever, sweats and marked dyspnea. For three months these symptoms of "pneumonia" continued and she left the hospital with little, if any, relief. She then entered another hospital where she remained

for ten weeks without seeing any marked improvement. Here she was told that inasmuch as her trouble was of a tuberculous nature, it were best that she seek climatic treatment. Directly from the hospital she went to the Adirondacks where she remained for ten weeks. Finding no relief, she returned to the city, applied to the Department of Health and was referred to the Montefiore Hospital as suffering from pulmonary tuberculosis.

On admission, October 9, 1919, we found her suffering from severe incessant cough, profuse expectoration of purulent material, at times fetid, or tinged with blood. Physical examination showed that the



FIG. 1.—Pulmonary abscess in lower lobe of left lung.

lower lobe of the left lung did not breathe: flatness, absence of vocal fremitus, feeble breath-sounds, and large, moist, consonating rales. The resonance elicited over the right upper lobe was impaired and the breath-sounds bronchial in character. We thus found one pulmonary lesion in the right apex and another more serious and extensive one, in the lower lobe of the left lung. There were also audible moist rales all over the chest, especially over the upper lobe of the left lung. Her temperature ranged between 100° afternoons and 98° F. mornings; the pulse-rate 85 to 95 per minute. The discordance between the extent and activity of the pulmonary lesion and constitutional symptoms was at once noted: She appeared

well nourished, her best weight having been 145 pounds and on admission it was 132, showing that despite the extent and activity of the disease lasting eleven months, there had not occurred that cachexia characteristic of phthisis of this activity, extent and duration. All this pointed to a non-tuberculous pulmonary process.

The radiographic plate (Fig. 1) showed a large, somewhat oval shaped, well defined shadow occupying the middle third of the left lung field. Evidences of pleuropericardial and diaphragmatic adhesions were also noted. In the right lung signs of hilus fibrosis associated with bronchial dilatation were found and also a number of fibrous bands running across the middle of the lung field. The fact that the radiographic picture of the right upper lobe was not that characteristic of tuberculosis, and that the heart was normal in size and appearance, confirmed the clinical opinion that the lesion was non-tuberculous.

The examination of the sputum, made eight times, failed to disclose any tubercle bacilli; various cocci, mainly staphylococci albus were found. The urine was negative, the blood-pressure 145 systolic and 100 diastolic, rather high for tuberculosis. A blood count also pointed against tuberculosis: 15,000 whites, and 75 per cent. polynuclears. Inasmuch as the radiographer insisted that there was fluid in the left pleura, though the physical signs—the presence of large, moist rales—were against this view, several exploratory punctures were made, one with a large caliber lumbar puncture needle, but all failed to bring out any fluid. On entering the patient's lung with a needle, about $\frac{1}{2}$ c.c. of thick, yellowish, foul-smelling pus, not unlike the matters she expectorated, was obtained.

An attempt was made by the writer to induce an artificial pneumothorax with a view of collapsing the left lung and thus assist in draining the abscess cavity, but owing to pleural adhesions no gas could be injected into the pleura.

On October 20 the patient was transferred to the non-tuberculous division of the hospital. The treatment was mainly postural. It was found that she sleeps on her right side, and that turning on her left side she coughs and expectorates profusely. Raising the foot of the bed and placing her on her right side for fifteen to twenty minutes several times a day, so that gravity helps in clearing the pulmonary cavity, has had a marked effect on her condition. She gained in weight, reaching 150 pounds, more than she ever weighed, and looks and feels well. Her temperature has been normal, for weeks, though now and then, when drainage is retarded, or when she neglects to recline on her right side for a day or two, the temperature rises one or two degrees, to decline again after postural treatment is applied. She was discharged March 18, 1920, greatly improved. She still coughs and expectorates, but her general condition is excellent.

CASE VI.—I. T., woman, aged twenty-seven years, admitted May 29, 1919. Her past history is of no importance, excepting perhaps that she had typhoid fever at the age of ten. Taken sick with influenza January, 1919, the initial symptoms were chills, fever, back-ache, cough, hemoptysis and pain in the right side of the chest. In a communication from the hospital, in which she was cared for at that time it is stated that she suffered from influenza complicated by bronchopneumonia. Because of the lingering lung lesion after five weeks' treatment, she was told that inasmuch as her trouble is of a tuberculous nature it is best for her to go to a mountainous climate. She went and remained there for six weeks, but the cough

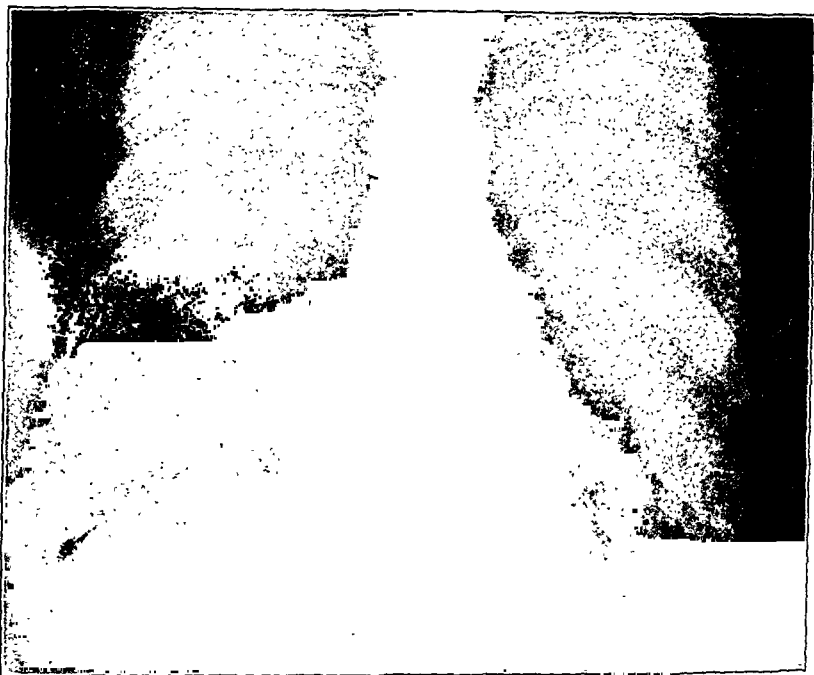


FIG. 2.—Abscess in lower lobe of right lung.

and profuse expectoration persisted, chills and fever, pains in the chest and weakness kept on annoying her. She returned to the city and was readmitted to the hospital where she was again told that her trouble was tuberculous, and she was referred to the Health Department. She was then admitted to the Sea View Sanatorium where she remained a short time and then transferred to the Montefiore Hospital under the writer's care.

On admission we found her apparently well nourished, though running high fever, of the continuous type, had frequent chills, sweats, pain in the chest, coughed and expectorated profusely. Repeated pulmonary hemorrhages occurred, some of which were quite copious. The sputum was malodorous. Physical exploration

of the chest showed that the main lesion was in the lower lobe of the right lung, over which the resonance was flat, the breath-sounds feeble, and large, moist rales and a friction sound were audible. The vocal fremitus was abolished over that area. However, the upper lobe of the right lung showed also pathological changes—impaired resonance and distinct bronchial breath-sounds. No changes at all could be discovered in the left lung. Repeated examinations of the sputum failed to show the presence of tubercle bacilli, but Gram-positive diplococci were found in abundance. The blood count showed 4,000,000 reds, 34,000 whites, and 75 per cent. lymphocytes; hemoglobin 70 per cent.

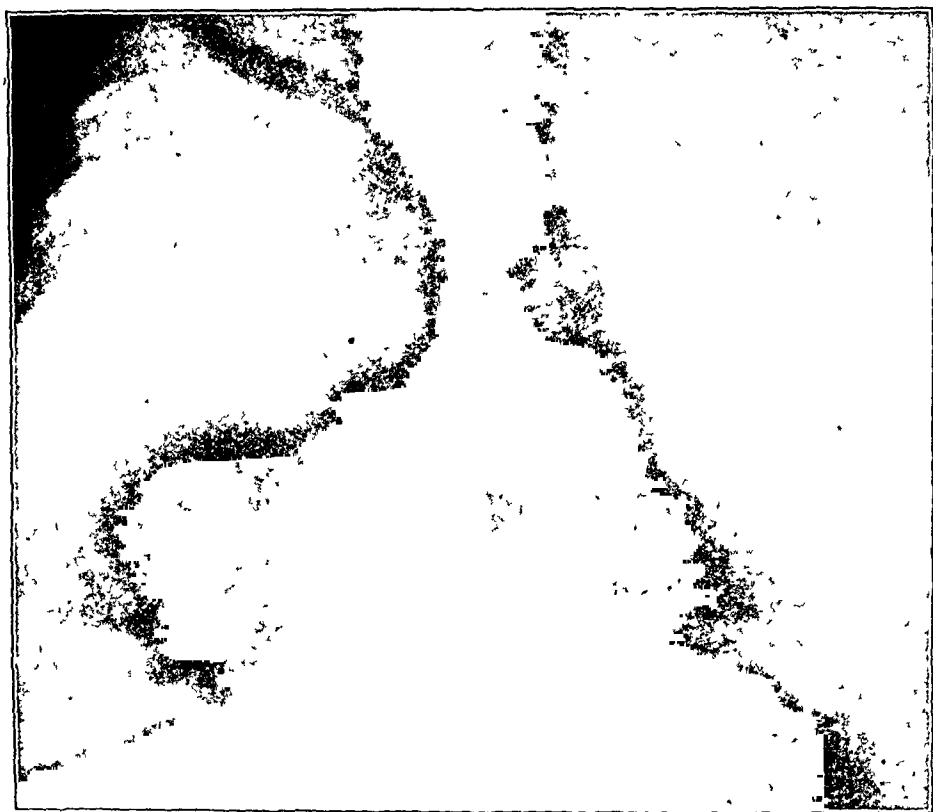


FIG. 3.—Same case as in Fig. 2. Complete collapse of right lung by artificial pneumothorax. The abscess cavity is seen surrounded by a thick capsule.

The radiographic plate (Fig. 2) also pointed against tuberculosis. The two apical fields were apparently free from distinct changes; a somewhat oval-shaped shadow obscured the middle portion of the right-basal field. The rest of the lungs were clear.

The clinical, bacteriological, radiographic and hematological data showed clearly that we were dealing with a lung abscess of influenzal origin. The usual treatment applied failed to be effective in relieving her symptoms, the incessant cough, profuse expectoration, the fever, the chills, etc., persisted. The following, culled from the bedside notes, give some idea as to the course of her ailment:

July 6, 1919. Severe pulmonary hemorrhage, lost about eight ounces of blood.

July 30. A more copious hemorrhage.

August 12. Patient has been bleeding profusely for three days. Horse serum administered with no visible effect.

August 17. Hemorrhage profuse and threatening. Induced an artificial pneumothorax, injecting 600 c.c. of air. Hemorrhage stopped promptly. On the three succeeding days further inflations of gas into the pleura were given, obtaining complete collapse of the right lung. The pulmonary hemorrhage was thus controlled for ten weeks. But no relief in the general symptoms was apparent. The fever, chills, cough, expectoration, etc., continued unabated. Considering the thick capsule around the abscess (Fig. 3) it is clear that the air in the pleura was not effective in obliterating the abscess cavity by compression. However, we continued the pneumothorax treatment and on October 15, signs of a pleural effusion, a hydropneumothorax,—succussion sound, metallic tinkle, flatness over the lower thirds of the right chest, etc.—made their appearance. Concurrently the pneumothorax was no more effective in preventing pulmonary hemorrhage; she began again to bleed profusely. Puncture showed that the effusion was purulent.

October 22. The septic fever, dyspnea, cyanosis, weakness, etc., not being relieved by the usual therapeutic measures, a thoracotomy was performed, and several quarts of foul smelling pus removed from the right pleura. Patient died four hours after the operation.

Resume.—In many patients attacked by acute epidemic influenza certain sequels are left in the respiratory tract after the acute disease had run its course. A large number remain with subacute rhinopharyngitis; some with general bronchitis, and now and then we meet with patients in whom the residual lesion is a localized bronchitis. When the latter affects an upper lobe of a lung, it is very difficult to differentiate it from pulmonary tuberculosis. When these sequels are instrumental in keeping the patient weak and debilitated for weeks or months, which is often the case; this, in addition to the cough and expectoration, may lead to a diagnosis of pulmonary tuberculosis. More serious pulmonary lesions are bronchiectasis and lung abscess which have increased in frequency since the last pandemic of influenza. Bronchiectasis remains in cases in which influenza was complicated by pneumonia or pleurisy, or both. The diagnosis is at times very difficult mainly because of the ancient notion that influenza is a strong predisposing factor to tuberculosis. When the lesion is found strictly localized in one of the lower lobes of the lungs, and this is the case in the majority, tuberculosis should be excluded for this reason alone. In those in whom the lesion is in an upper lobe, only repeated sputum examination decides, though the fact that the disease began with influenza,

that emaciation is not pronounced, that fever is lacking, the pulse-rate is normal, and that there is obtained clear resonance above the clavicle, etc., should be counted against tuberculosis. The more severe lesions in which pulmonary abscess remains after influenza the diagnosis may be made along the same lines as in bronchiectasis, and in addition note should be made of the fact that the sputum is abundant, at times fetid, the fever continuous or undulating, the pain in the chest and the physical signs, all of which combine to clear up the diagnosis. If several examinations of the sputum fail to disclose tubercle bacilli the diagnosis may be safely made. Leukocytosis, with an increased proportion of polynuclear cells have the same significance.

STUDY OF A CASE OF UNEXPLAINED LOW CARBON DIOXIDE COMBINING POWER OF THE BLOOD.

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AND

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THE following case is reported because of the persistent occurrence of a low carbon dioxide combining power of the blood and an increase in the rate and depth of respiration in an individual in whom no adequate explanation for these phenomena could be discovered. The patient's chief complaint was shortness of breath and a feeling that his heart beat fast; the abnormal respiration was sufficiently marked to attract immediate attention when one approached the patient. It was this observation which led to the further special study of the case as well as the fact that the physical examination revealed no cause for the obvious increase in respiratory frequency; nor did the routine laboratory studies reveal any of the disease conditions which we are accustomed to expect as leading to dyspnea. No justification for a diagnosis of cardiac, pulmonary or renal disease was found, nor was there any evidence of diabetic acidosis; in fact, no evidence of disturbed acid-base equilibrium other than the constantly low plasma carbon dioxide combining power. There was no fever.

In brief, the patient presented an unusual picture which we are unable to explain, and we are reporting the facts without attempting

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to draw any conclusions. Undoubtedly a reasonable explanation exists, to become apparent only after further facts are known.

CASE REPORT.—G. H., male, aged sixteen years, entered the University Hospital on February 9, 1920, complaining of shortness of breath and a feeling that his heart beat fast. The history in brief was as follows: He was in perfect health until about five weeks before admission, when he had run for over an hour without any previous training. He was accompanying a boxer who was training, and they ran "at least five miles." There was no special discomfort at the time, but three days later he became conscious of the beating of his heart. A week later he had an acute attack of dizziness and vomiting, which continued for two days. He stated that he had not been well since the overexertion in running, and he claimed to have lost ten pounds during the two weeks prior to admission. Previous medical history was negative and there was nothing of importance in the social or family history.

The patient was a healthy looking individual, obviously a mouth-breather. It was noted at once that the breathing was more rapid and deeper than normal; the rate varied between 24 and 32 to the minute. The hands and fingers were somewhat cyanosed, but not markedly so; the blood-pressure was low: systolic 96, diastolic 68. Definite tonsillar enlargement was present and also a slight general adenopathy. In all other respects the physical examination was negative. Repeated examinations of the heart by several examiners and by fluoroscopy and electrocardiography revealed no alteration from the normal. The lungs were normal by physical examination; roentgenograms revealed no pulmonary pathology nor any mediastinal abnormality. Neurological examination was negative.

The routine laboratory examinations were as follows: Blood count: Erythrocytes, 4,410,000; leukocytes, 7000; hemoglobin, 71 per cent. Differential count: Polymorphonuclear neutrophils, 73 per cent.; lymphocytes, 22 per cent.; large mononuclears, 4 per cent.; transitionals, 1 per cent. The serologic test for syphilis was negative. As is our custom, specimens of urine were sent to the laboratory on the first, third and fifth mornings after admission. These showed striking variations in the concentration, albumin content and microscopic findings. Such changes are familiar to all hospital physicians and result at least in part from the increase in fluid intake incident to hospital care.

Color.	Sp. gr.	Albumin.	Microscopic.
1. Dark amber	1029	Heavy cloud	Light and dark granular casts.
2. Amber	1015	Very faint trace	0
3. Straw	1007	0	0

In all other respects the examinations were negative. On the day of the third specimen the phthalein elimination was 60 per cent.

in two hours and the blood-urea nitrogen was 15 mg. per 100 c.c. of blood.

Other special examinations which should be mentioned included a negative examination of the eye-grounds and negative roentgenograms of the pituitary region. Roentgenograms of the teeth revealed an abscess at the root of a molar tooth.

The following table will detail the further study of the case:

1920.	Sod. bi-carbon., gm.	Blood plasma, CO ₂ vol., per cent.	Urea N., mg. per 100 c.c.	Urine.				
				Amount, in c.c.	Specific gravity.	Reaction.	NH ₄ N.	Titrateable acidity, N/10 NaOH
Feb. 14	5	29.0	15					
15	20							
16	5	42.5						
17	2840	..	Acid	0.30	249.2
18	2540	..	Acid	0.24	223.1
19	..	48.2	..	3000	..	Acid	0.44	368.0
20	..	53.0	15	2800	..	Acid	0.59	396.0
21	..	52.0	..	4000	..	Acid	0.59	747.0
22	5000	1.004	Acid	0.26	571.0
23	..	47.0	..	4760	1.005	Acid	0.36	786.0
24	..	42.0	..	3850	1.008	Acid	0.36	857.0
25	..	47.0	..	3620	1.008	Acid	0.36	
26	..	46.0	..	3400	1.004	Acid	0.33	439.0
27	20	46.0	Spec. lost	
28	20	48.0	..	3870	1.007	Acid	0.22	104.5
29	20	3160	1.008	Acid	0.20	104.5
Mar. 1	20	50.0	..	2310	0.008	Acid	0.25	
2	25	54.0	..	3920	1.008	Acid	0.18	170.5
3	20	59.0	12	2660	1.010	Sl. alk.	0.12	Neutral
4	25	55.0	..	2230	1.011	Sl. alk.	0.18	120.0
5	1910	1.008	Acid	0.27	176.0
6	..	49.0	Spec. lost	
7	2320	1.009	Acid	0.42	288.0
8	2680	1.010	Acid	0.46	171.0
9	..	54.0	..	1780	1.010	Acid	0.21	363.0
10	940	1.016	Acid	0.31	284.0
11	..	55.0						
12	..	55.0	12					
15	..	52.0						
17	..	43.0						
18	..	48.2	12					
22	..	47.9						
23	..	47.0						
27	..	49.0						
30	12					
April 1	..	53.0						
6	..	52.0						
14	..	53.0	12					
June 1	..	55.0	17					

Interest was aroused by the report that the plasma carbon dioxide combining power was reduced to 29 volumes per cent. and a corresponding low alveolar carbon dioxide tension. No observations

were made to determine the influence of the low CO_2 combining power of the plasma on the power of the hemoglobin to combine with oxygen.

The examination of the data contained in the protocol together with an absence of both a ketonuria and a glycosuria and the presence of a normal blood sugar immediately excluded diabetes as the cause of the low CO_2 combining power of the plasma.

The examination of the urine for lactic acid was negative for any abnormal production of this acid.

We feel that nephritis, as has been previously stated, can be eliminated by the constant absence of urea retention and the normal phenolsulphonephthalein elimination. Albumin and casts were found in the first examination of the urine, but all subsequent examinations were negative. Although a marked polyuria and a corresponding low specific gravity were present for a number of days the kidneys were able to concentrate, as was shown by the first urinary examination when the specific gravity was 1029, and on April 27, 1920, when the intake of fluids was greatly restricted, with a result that the output was reduced to less than 500 c.c. per twenty-four hours and the specific gravity raised to 1029. We do not feel that the polyuria is especially peculiar to the condition because of the great ingestion of fluids, particularly water and milk. The striking feature of the case is the low CO_2 combining power of the plasma with the constant normal output of ammonia nitrogen and a normal titratable acidity, except from February 20 to February 24, when the titratable acidity was above normal. The cause of the increased titratable acidity at that time is unexplained. Although a total of 30 gm. of bicarbonate of soda was given between February 14 and the morning of February 16, we feel that it did not influence the ammonia nitrogen and titratable acidity on the subsequent days, particularly in view of the continued low CO_2 combining power of the plasma.

Henderson¹ has shown that hyperpnea may cause a marked lowering of the carbon dioxide combining power of the plasma with a normal urinary ammonia and titratable acidity. We investigated the possible application of this idea to our patient, assuming that the rapid, deep breathing was due either to an oversensitive respiratory center or stimulation of the center by a neoplasm, perhaps of the pituitary, in view of the polyuria. Negative roentgenographic findings excluded a pituitary tumor as the cause. If due to over-ventilation then the depression of the respiratory rate should raise the blood CO_2 combining power with no ill-effects, such as would result if due to the usual clinical causes of acidosis. To test this possibility, morphin sulphate was given hypodermically from

¹ Jour. Biol. Chem., 1918, xxxiii, 345, 355, 365.

February 18 to February 21. By February 21 the respiratory rate was reduced to 16 per minute, and during this period the blood CO_2 reached its highest figure, except early in March, when the high figure was due to the administration of sodium bicarbonate. Unfortunately the specimen of blood which was taken just before the beginning of the administration of morphin sulphate was lost, due to an accident. After the affects of the morphin sulphate had ceased the blood CO_2 again fell. No ill-effects on the patient were observed during this experiment.

Although these experiments seem to admit the possibility of overventilation as the cause of this unusual phenomenon in the patient, we do not feel that the data at hand is sufficiently conclusive to permit this or any positive diagnosis. The sensitiveness of the respiratory center was tested on March 3, after the blood CO_2 had been raised to normal, by the administration of sodium bicarbonate from February 27 to the date of the experiment. The method employed was to have the patient breathe normal air and then air containing 5.2 per cent. of CO_2 , recording the rate and depth of the respirations on a kymograph. It was found that the breathing of air containing 5.2 per cent. of CO_2 caused a turn-over of air twice that observed before the CO_2 was increased. This is considered a normal reaction for that concentration of CO_2 .

Other possible explanations have to be considered, but none appear satisfactory. Hysteric tachypnea, such as was described by S. Weir Mitchell, and such as is not infrequently observed clinically, is apparently ruled out by the persistence in this case of the respiratory rapidity during sleep. The acute attack of indigestion with vomiting can scarcely be considered prolonged enough to have disturbed the patient's acid-base equilibrium for so long a period, nor were the alterations in this case those seen after vomiting, starvation or in "cyclic vomiting," such as ketonuria, etc.

EMPYEMA THORACIS: AN ANALYSIS OF FIFTY-SIX CASES IN THE INDIANA UNIVERSITY HOSPITAL.*

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EMPYEMA literature of the last two years is voluminous enough to give the average reader mental anorexia. The subject has necessarily been clouded with uncertainty, so rapid have been the changes in conception of both pathology and treatment. The aim of this

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analysis of 56 cases is not only to tabulate the results, but, further, to ascertain by comparison with other series the soundness of our position on the question.

Mortality. Our cases have been civilian and of both sexes, varying in age from sixty-four years to four months. The average, 22.8 years, is not far from 21.6 years, Ransohoff's¹ civilian average at the Cincinnati General Hospital. Few of our cases have had the soldier's rugged constitution to help combat infection, which in a measure justifies our 7.1 per cent. mortality in the face of the 4.3 per cent. death-rate of the Empyema Commission.³ Then, too, one of the deaths was more, strictly speaking, a traumatic pyothorax, the patient (a man of sixty-four) dying eight weeks following a gunshot wound of the lung. Another one of our fatal cases entered the hospital moribund and died a few hours after admission, physical examination having revealed, aside from the empyema, an active Neisserian infection, a fulminant nephritis and associated general edema. The third death was in a child of three and a half years, whose empyema followed a virulent measles pneumonia. In the fourth death, pleural pus pockets were complicated by a large lung abscess. That our death-rate does not approach the 28 per cent. of Vaughan,⁴ the 12 per cent. of Eggers⁵ and the 15.6 per cent. of Willard Stone's second series⁶ is probably referable to the fact that the cases represent no single epidemic, and hence perhaps not such virulent infection. On the other hand many have been eleventh-hour emergencies: the cases of empyema gravitating to a state charity hospital we have found often to be cases that the home doctor has "given up for dead."

Clinical Data. Past history of nose, throat and chest troubles has been infrequent among our cases. (Percentages are noted in Chart I.) These low figures only reemphasize the long recognized fact that past history and pulmonary predisposition are hardly important factors in the etiology.

Eggers was able to develop a history of antecedent pneumonia in almost all of his cases. While 44 per cent. of our cases followed frank pneumonia and 22 per cent. influenzal pneumonia, gunshot wounds, pertussis and measles pneumonia have also been precursors of the condition. (See Chart II.) In 8 per cent. there were other suppurative body foci, *e. g.*, pus appendix, cellulitis of the leg, gluteal abscess, etc. (In 20 per cent. of the cases there was a family history of tuberculosis.)

Diagnostic Features. *Temperature.* Though Vaughan has noted cases that were completely afebrile, picked up only on routine examination, all of ours have shown a perceptible amplitude (minimum 1 degree, maximum 7 degrees, average 3.85 degrees).

Pulse-rate. The importance of a high pulse-rate—already emphasized by Stone—we have had occasion to observe in this series. The general average of pulse-rates was 104—none of the cases showing a rate below 80.

Leukocyte Count. Our maximum white blood count was 28,000, minimum 8000, average 17,000.

X-ray. In a certain number of cases the fluoroscope has been of great value, but in others quite deceptive. Our observations certainly agree with those of Vaughan, that it is in interlobar empyema that fluoroscopy is of the greatest value.

Urine. Less than half of the cases have voided normal urine (32 per cent.). The findings are conveniently tabulated:

Albumin	14 per cent.
Albumin and casts	30 "
Albumin and pus	18 "
Albumin, casts and pus	4 "

Physical Signs. The four physical signs of greatest diagnostic value in the series have been (1) lagging or retraction of the affected side (in 88 per cent. of cases); (2) dulness (84 per cent.), (3) distant or absent breath sounds (80 per cent.), (4) diminished tactile or vocal fremitus (74 per cent.). Grocco's triangle and cardiac displacement have been surprisingly rare physical signs.

The chronicity of many of the cases has resulted in the frequency of other symptoms less common in military practice; 26 per cent. of our cases showed very extreme emaciation. Only two of these had other cause for the symptom than the present trouble, and these two were tuberculous. There was definite hypertrophic pulmonary osteo-arthritis in 26 per cent. of the series. In half of this number the process was over a year old when we received the cases. Sinus scars were present in 22 per cent. of the series.

Treatment. (a) *Underlying Principles.* Graham and Bell⁷ have ingeniously shown, in both dog and man, (1) that the normal thorax is in reality a single cavity, the mediastinum acting much as a rubber membrane in dividing it into two compartments, each one of which is necessarily sensitive to changes in pressure in the other; and (2), that the normal pleural cavity will tolerate an opening of a certain determinable size (about 2 by 5 cm.). In pneumonia or other conditions producing diminution in available breathing space there is also diminution in the size of the thoracotomy wound that can be tolerated. In view of these factors it is argued that with too large an opening an alarming situation can develop—pneumothorax, with pulmonary collapse on the open side and bulging of the mediastinum to the opposite side with subsequent excursion limitation and consequent embarrassment of the sound lung (Eggers). This is claimed to be the train of events after opening the general pleural cavity. Whether or not this sequence of conditions actually occurs is after all of academic rather than practical interest, since opening of the general pleural cavity is a procedure never indicated in the treatment of empyema.

Quite different are the factors to be reckoned with in the opening

of an empyema cavity. The pathologic processes generating an empyema include the walling off of a pleural compartment in which the pus is enclosed.* Opening this does not mean opening the general pleural cavity, which is excluded by a definite barrier of adhesions. It is generally acknowledged by the best authority^{8 3 5 6} that until this barrier is well organized, aspiration is the only scientifically sound and thoroughly safe method of removing fluid. Vaughan even advises no other surgical interference than repeated aspiration as the case progresses, provided the patient is clinically gaining ground; and Stone reports 11 per cent. of 310 cases cured with no further drainage. In one of our cases, a boy of four years, with bilateral empyema, aspiration alone has taken care of one side.

Though the intercostal trocar and catheter (with negative pressure) are theoretically permissible and in some cases have been successfully used at this stage of adhesion formation, there is always the danger of a flaw in apparatus, a break in technic, with the resultant serious accident, pneumothorax. The danger is, of course, only exaggerated if the other lung is pneumonic.⁹ When once the cavity is walled off the problem becomes one of simple drainage, and as Hartwell¹⁰ emphasizes, collapse of the lung will not follow open operation, for the very obvious mechanical reasons already stated.

(b) *Operative procedures.* These may be grouped and considered thus:

I. Acute Empyema.† A. *Aspiration.* Aspiration, the treatment *par excellence* during the formative stage, is occasionally sufficient in well-encapsulated accumulations. It was the only measure in 3½ per cent. of our cases. In one the puncture was the last resort on a patient who entered the hospital moribund and died the same day. Another, delivered ten days before, made an uneventful recovery after several taps. Reference has already been made to the third case, a boy of four, with bilateral empyema.

B. *Open Intercostal Drainage.* In 2 cases of rather abortive type intercostal drainage was deemed sufficient. One was irrigated for several days with normal salt solution. Both left the hospital three weeks after operation.

C. "*Closed Methods.*" Moschowitz,¹¹ introducing an intercostal tube of good size (preferably in the eighth interspace, posterior axillary line) secured by suction probably the best drainage of any of the closed intercostal methods. Diederich's¹² method in principle is very similar. Mazingo¹³ introduces the added feature of glycerin-formalin injection. In considering these methods the pathologic conditions should be kept clearly enough in mind to avoid the mistaken conviction, only too often expressed, that negative pressure

* Vaughan has shown that this encapsulated empyema is the dominant type.

† Since differentiation depends on so many features, the terms *acute* and *chronic* in referring to empyema are certainly unhappy. We use them arbitrarily as follows: *acute* applying to cases never before drained; *chronic*, those with sinuses.

is preventing pulmonary collapse. The value of negative pressure at this stage is only in mechanically aiding in drainage. Adhesions have by this time precluded the possibility of collapse. It should also be remembered there is no excuse for this type of drainage before the empyema is excluded from the general pleural cavity.

Müller's¹⁴ very excellent commentary on these "closed methods" is worthy of repetition in full: "It seems to me that there is but little difference in the methods of Mozingo, Diederich or of Moschcowitz. They will cure a certain percentage of the cases, but are liable to pocketing, persistent cavity or relighting of latent infection. They will be most successful in the streptococcic group. The method of Moschcowitz is the best, because he uses the largest tube and therefore gets the best drainage, that of Mozingo the worst, because he gets no drainage at all but depends on chemical sterilization for the results."

Another very significant paragraph of Müller's review reminds that closed methods fifteen years ago had a vogue and then went into the discard (Shiller¹⁵). This item in the history of empyema is certainly suggestive and should stir in the profession a wholesome skepticism until the next five years show closed method cases to be non-recurrent.

D. Rib Resection. Since copious drainage the first twenty-four hours is of the utmost importance, and anything less than thorough drainage is inexcusable, rib resection has seemed to us the only safe method of treating well walled-off cases. This opinion, shared by many others,^{3 5 6 10 16 17 26} has the sanction of years and has already outlived one "closed method" era a decade or more ago.

Sixty per cent. of the cases in this hospital have been so treated, the seventh and eighth ribs being the commonest sites of operation. Two resections were in the anterior, six in the posterior, and twenty-two in the mid-axillary line. The observation of Keyes,¹⁶ that posterior axillary line wounds offer the best drainage seems to be substantiated by these results, for the average postoperative stay of the midaxillary cases was five weeks, anterior axillary four and a half weeks, posterior axillary four weeks. These figures compare favorably enough with the postoperative forty days of Diederich's closed method and the five or six weeks of Rodman.¹⁸

Among the objections raised to rib resection have been pain, serious and often fatal intercostal vessel hemorrhage, lung collapse, etc. Lung collapse we have never observed in a single case of this series. We cannot conceive of such an accident occurring if ordinary care is taken to await encapsulation, the existence of which aspiration, clinical history and physical signs will clearly evidence. The danger from hemorrhage we believe overestimated. In what cases of this series the intercostal vessels have been injured, bleeding has stopped spontaneously, without ligation, and soon enough to occasion negligible operative delay. In our experience thorough infiltra-

tion of the skin and blocking of the intercostal nerves with novocain renders rib resection a painless operation. One recent case, a physician, assures us that his side was completely anesthetic during the entire procedure. (Of course, a rib snapping in the rongeurs is hardly a reassuring sound and will ever be disconcerting to the neurasthenic!)

E. Subsidiary Therapeutic Measures. 1. Irrigation: Dodge and Eggers are skeptical about irrigation, and Babcock,¹⁹ on departure from Fort McPherson, left 80 empyemas still draining which had been so doing for a year despite Dakin irrigations. However, the results of Stevens²⁰ would seem to indicate that the judicious use of Dakin's solution is of value. Of his 123 cases, 56 treated by simple drainage showed 25 per cent. recurrence; 67 treated by drainage followed by Dakin irrigations showed only 12 per cent. recurrence. Müller's caution is timely, that Dakin's solution must be evaluated as only a surface disinfectant, not capable of sterilizing the depths of infected pleura. Irrigation (with normal salt solution) has been used in but one of our cases.

2. Glycerin-formalin Instillation: Glycerin and formalin, originally used years ago by Murphy, has been instilled according to varying technics by Sherrill,²⁵ Diederich, Mözingo, and Rinehart. Diederich believes the practice of little advantage over simple aspiration. We have had no experience with this method.

3. Medical Treatment: Medical treatment in this series has consisted of little more than morphin p. r. n. immediately after operation and a 3000 to 4000 calory diet. Eggers mentions the importance of the patient's position in favoring drainage. In our experience the first notch of the Gatch bed offers a valuable alternative to the supine posture.

II. Chronic Empyema. Under this head we include cases (a) with persistent draining sinuses following previous operations and (b) with scars and reaccumulations of pus. Treatment in these cases has been directed solely toward one end—the obliteration of the cavity. In some instances it has been sufficient merely to resect ribs and allow parietal pleura to collapse into the depths of the cavity; in others decortication has been necessary because of pleural rigidity. The series consists of 11 cases; 4 of these had been operated on prior to admission to this hospital and had an average past duration of two years. In these, operation consisted in removing subperiosteally (under general anesthetic) portions of from three to five ribs over the cavities. The average post-operative hospital stay was six and a half weeks.

In the seven remaining cases rib resection was done as a deliberate preliminary step toward thoracoplasty, the cavities at initial operation presenting anatomic features which made the necessity of further operation quite obvious. The average period between operations was five weeks. All the secondary operations but one

were done under general anesthetic (ether). (Wattenberg²¹ also prefers general anesthesia for secondary operative work but uses nitrous oxide.) None of the eleven cases was in the hospital longer than eight weeks after operation—and the average stay was four and a half weeks. There was one death—a thoracoplasty mortality of 9 per cent.

Years ago Schede²² claimed that when pleurisy becomes purulent a thick fibrin membrane covers the pleura, but that this can be stripped off months or even years later, leaving a relatively normal pleural surface. Often as early as the tenth day (Lilienthal²³) this inflammatory covering of the visceral pleura, having become tough, can very materially interfere with the lung expansion. During the earlier stages of the process this immobilization is protective. Later the indication for lung splinting disappears. At this stage Lilienthal, under a general anesthetic, separates the ribs, incises the pleural cavity and mobilizes the lung by freely incising the expansion-limiting membrane around the visceral pleura. The Lilienthal operation in the hands of Whittemore² has given slightly lower mortality than ours— $8\frac{1}{4}$ per cent. of 12 cases. But Lilienthal himself²⁴ has reported 3 deaths in one series of 20 cases.

The Tinker-Wattenberg procedure would seem to offer a less dangerous alternative to thoracoplasty, but we have not yet had occasion to try the method.

Summary. *Clinical Data.* In a series of 56 cases of empyema thoracis at the Indiana University Hospital the mortality has been 7.1 per cent. Most cases followed pneumonia, though injury, pertussis, measles, etc., have also been antecedent conditions. Twenty per cent. had familial tuberculosis, but a negligible percentage gave personal history of pulmonary predisposition.

Signs and Symptoms. The cases showed an average febrile amplitude of 3.8 degrees, average pulse-rate of 104 (none below 80) and an average leukocyte count of 17,000. Less than one-third voided normal urine—and 30 per cent. showed definite evidence of renal involvement.

Lagging or retraction of the affected side, dulness, distant or absent breath sounds, and fremitus absence were the outstanding physical signs (in the order of their frequency of occurrence).

Treatment. In view of the fact that "closed methods" (and we do not include aspiration here!) would seem based on a faulty conception of the pathologic physiology of the chest in empyema, the treatment of acute cases in this series has been palliative aspiration until cicatricial exclusion of the general pleural cavity has made rib resection the operation of safety and choice. Sixty per cent. of these cases have had rib resections—usually the seventh or eighth in the midaxillary or posterior axillary lines. The average post-operative hospital residence has been four and a half weeks, the

posterior axillary line cases leaving the hospital first. We profess no experience in glycerine-formalin instillation.

In chronic empyema the aim has been cavity obliteration by subperiosteal rib resection and at times parietal pleura extirpation. Our mortality with this plan of treatment is 9 per cent. in 11 cases; slightly above the $8\frac{1}{2}$ per cent. (in 12 cases) of Whittemore, who performs the Lilienthal operation. However, Lilienthal with his own method has reported 3 deaths in 20 cases.

The writer wishes to acknowledge many helpful suggestions, during the preparation of the work, from Dr. W. D. Gatch, Professor of Surgery.

CHART I.—PREDISPOSING PAST HISTORY.

Total number of cases	100 per cent.
Cases with frequent chest colds	8 "
Cases with frequent head colds	6 "
Cases with repeated sore-throat	6 "

CHART II.—ANTECEDENT TROUBLE.

Total number of cases	100 per cent.
Frank pneumonia	44 "
Influenzal pneumonia	22 "
No definite clinical entity	22 "
Gunshot wound of chest	4 "
Whooping-cough	4 "
Measles pneumonia	4 "

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A RECORD OF EXPERIENCE WITH CERTAIN PHYSICAL EFFICIENCY AND LOW OXYGEN TESTS.

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THE student of aviation medicine has been confronted with the problems of protecting the flier against the effects of physical deterioration and the effects of altitude, low barometric pressure and deficiency of oxygen.

The call for a measure of health and physical fitness comes from the fact that the aviator has need of all his physical energy and intelligence. Flying requires an active, well-balanced, decisive mind and sound, quick, reflex actions. The aviator must be able to recognize at once the slightest difficulty with his machine. His senses must give him accurate information of changes in the rhythm of his motor, of the sing of air across the wires of the machine and of his position in space. He must be master of his impressions and ready to make prompt decisions in a calm, cool manner. It is now clearly recognized that the aviator's reactions to stimuli are slowed down or disturbed by disease, worry, fatigue, excessive use of alcohol and other excesses. Such influences may cause a delay of a second, or part of a second, in correcting an error in difficulties in the air or in landing which may mean the difference between a crash and safety. The medical adviser requires tests that will reveal the degree of loss in efficiency in order that he may intelligently say when the aviator should not fly.

The ability to endure altitudes well and without loss in efficiency is dependent upon the ease and quickness with which certain adaptive adjustments are made. There are marked individual differences in this respect. Some men adjust so well that they are not disturbed by heights which render the average person quite inefficient. A few men fail entirely to respond to altitude and become inefficient at relatively low altitudes. The flight surgeon finds it advantageous to have the fliers under his supervision, classified as to their ability to compensate to the effects of altitude.

In this paper we shall report the results of a study of 128 aviators who were subjected to the Official Altitude Classification Examination used by Air Service Section of the U. S. Army; to five of the standard respiratory tests used by the Royal Air Force in England, and to a careful overhaul by a neurologist, internist, ophthalmologist and otologist. The clinical examinations showed thirty-one of these aviators to be stale or physically below par.

In England, in the Royal Air Force, under the guidance of Lieut.-Colonel Martin Flack¹ ² a set of simple physiologic tests was devised to indicate subjects who were likely to suffer from discomforts in the air, such as headache, giddiness, fainting, nausea, vomiting, pressure in the head, blood rushing to the temples, palpitation of the heart, etc., symptoms which might be due to lack of proper oxygenation of the blood and likely to render the man unfit for flying.

The tests grew in number with experience and the application of them was extended to detect flying stress and fatigue. More recently Flack has stated that he believes them to be of use in determining the physical efficiency of an individual. He emphasizes that these tests are not designed to supplant the work of the clinician in any way, and when a man is reported as physically unfit on these tests it does not mean that the work of the physician is finished but that it is beginning.

If the subject does not come up to standards then the neurologist, cardiologist or general physician will find that something is wrong with him. The tests, it is believed, give indications for such overhaul.

Altitude and Physical Efficiency. Tests Used in the Royal Air Force in England. In a complete physiologic examination seven distinct sets of observations are made upon the pilot. These include (1) the response of the pulse to a standard exercise, (2) time the breath is held in seconds after a full expiration and full inspiration, (3) time the breath is held after the standard exercise, (4) vital capacity, (5) extrapulmonary reserve as represented by the factor respiration rate multiplied by ventilation per minute divided by the vital capacity, (6) expiratory force and (7) the "fatigue" test. The value of the tests depends on all being carried out in the same way on all occasions.

The technic and interpretations of five of the tests may be summarized as follows:

1. In holding the breath the seated subject is instructed to expire once as deeply as possible then inspire fully and hold the breath as long as possible. The subject is watched to determine the degree of suffusion and color of the face. The reason for giving up is carefully noted. It is claimed that the breath-holding shows whether there is "oxygen want" and thereby whether the individual is likely to do well at high altitudes. If dizziness, blurred vision, etc., occur under forty seconds the candidate is debarred from flying. Good pilots manage sixty seconds, and it is maintained that all should be able to hold a minimum, in three times, of forty-five seconds.

¹ Lancet, 1919, i, 210.

² Anderson: The Medical and Surgical Aspects of Aviation, London, Oxford Press, 1919, p. 55.

2. In measuring the vital capacity the subject is asked to fill his chest and blow hard through a meter, taking precautions against overblowing the meter. The minimum vital capacity is fixed at 3000 c.c. It appears that no account is taken of the size of the man. It is maintained that a capacity below 3400 c.c. and inability to hold the breath for more than forty-five seconds contra-indicates high flying.

3. Bazett,³ who formulated the respiratory reserve factor, suggested that men with a large vital capacity, a low consumption of air per minute and a slow respiratory rate tolerate high altitudes better than others. He found that the average figure for the good type of flyer is 24.1, for the bad 46.3 and for the uncertain 36.8. A figure of 30 has been taken as the standard, those above this being relatively bad for high altitudes.

4. For the determination of the expiratory force a U-tube manometer, filled with mercury, is used. The subject is asked to blow the column steadily as high as possible and not to swing it up by the momentum of the mercury. It is believed that this is a measure of fitness and of the tone of the abdominal wall. The average normal is about 105 mm. Hg. It was found that pilots suffering from flying stress can often only blow 40 mm. If the test is about 80 the pilot is considered suitable for only 'low flying, and if much below is probably in need of a rest from flying altogether.

5. The fatigue test is another with the U-tube manometer. The subject is asked to empty the lungs, take a deep breath, blow the mercury to the height of 40 mm. and hold it there without breathing for as long as possible. According to one hypothesis the test is an indication of the tone of the respiratory center. The average normal time of many cases is fifty seconds. Below forty seconds is considered unsatisfactory and indicates that probably the subject is fit only for limited flying or is in need of a rest.

It is not claimed that each test is capable of rigid application but that it is the combination of the tests that is important.

Altitude Classification Examination. The altitude test for the classification of aviators that has been used by the U. S. Army is described in the *Manual of the Medical Research Laboratory* (p. 215). In this test the aviator rebreathes for a period of twenty-five to thirty minutes through the Henderson rebreathing apparatus 52 liters of air from which the carbon dioxide of the expired air is removed by an absorbent. As the oxygen gradually and progressively decreases the subject is under observation by a physiologist, psychologist and clinician. The physiologist determines the rate and volume per minute of breathing, the pulse frequency and the systolic and diastolic arterial pressures. The psychologist records changes in

³ Report of the Air Medical Investigation Committee, London, 1918, No. 6, p. 7.

attention and motor coördination until the subject reaches the point of complete inefficiency or until the clinician finds that the condition of the circulation makes prologation of the test undesirable. A few subjects exhaust the oxygen to 6 per cent. or a little lower, many reach 7 per cent., while poor subjects may become mentally inefficient or faint at considerably higher percentages, 9 to 12. A majority of all men examined gave the first physiologic evidences of compensation to the reduction in oxygen at between 16 and 14 per cent. of oxygen.

Our data for the 128 aviators have been examined by statistical methods and these are summarized in Table I:

TABLE I.

	No. of cases.	Arithmetical mean.	Probable error.	Correlation with oxygen.	Correlation with oxygen consumption rate.
Final oxygen percentage . . .	128	7.59	$\pm .07$		
Length of run in minutes . . .	128	24.15	$\pm .14$	$-.51 \pm .04$	
Vital capacity in liters . . .	128	4.33	$\pm .36$	$-.06 \pm .06$	$.20 \pm .06$
Breath held in seconds . . .	127	67.84	± 1.22	$-.18 \pm .06$	$-.03 \pm .06$
"Fatigue" test in seconds . . .	122	52.20	$\pm .84$	$-.12 \pm .06$	$.13 \pm .06$
Expiratory force in Hg. mm. . .	123	123.01	± 1.82	$-.11 \pm .06$	$.10 \pm .06$
Extra respiratory reserve factor	126	40.55	$\pm .78$	$.025 \pm .06$	

The averages as determined in England by the examination of healthy pilots in the Royal Air Force were: Vital capacity, 3800 c.c.; breath-hold, sixty-six seconds; expiratory force, 110 mm.; "fatigue" test, breath-holding while sustaining by blowing a column of mercury at 40 mm., fifty-two seconds. It will be seen that our American group averaged above the English group in vital capacity, expiratory force and breath-holding, while in the "fatigue" test the two groups were the same. In the American group there were 31 men found to be stale or physically below par by clinical examiners.

The Relation of the Ability to Hold the Breath and the Endurance of Low Oxygen. If the time the breath can be held should prove to be an index of ability to respond to the influence of low oxygen it would serve as a simple means of classifying aviators for altitude flying.

Flack has stated his opinion of the breath-holding test as follows: "The test was originally designed to show whether there was 'oxygen want,' and I still believe the test does show the subject who would suffer from 'oxygen want.' From my experience I found that people who were likely to suffer from 'oxygen want' would give up after a very short time in holding the breath and would almost invariably return an abnormal answer. A normal answer would be that the subject 'had to give up,' 'felt he would burst,'

an abnormal answer that 'the blood rushed to his head,' 'things became blurred,' etc."

We have determined that the coefficient of correlation between the time the breath was held and the lowest percentage of oxygen tolerated by 127 men was only -0.18 ± 0.06 . This no doubt indicates that the compensation to a gradually decreasing oxygen supply is dependent upon other factors that exert a more profound influence than conditions that obtain during breath-holding and that the power to hold the breath is at the best of only minor importance as a measure of ability to endure low oxygen.

The average time for holding the breath was sixty-eight seconds, the longest time was one hundred and twenty-eight seconds and the shortest thirty seconds.

There were ten men who managed to hold their breath only forty-five seconds or less, the minimum allowed by the English standard, and of these six remained fairly efficient down to 7.5 per cent. of oxygen, one even reached 6 per cent. Four of the men failed between 9.8 and 8.4 per cent. oxygen.

Two groups of breath-holding cases of 13 and 12 each illustrate well the wide range in ability to compensation to low oxygen. There were 13 men who managed to hold the breath between sixty and sixty-five seconds, of these 2 became inefficient in the rebreathing altitude test before reaching 9 per cent. of oxygen, 3 did not reach 8 per cent., 4 failed between 8 and 7 per cent., while the last 4 held on to between 7 and 6 per cent. The group of 12 that held the breath for from seventy to seventy-five seconds became inefficient as follows: 2 before reaching 9 per cent., 3 between 9 and 8 per cent., 3 between 8 and 7 per cent. and 4 between 7 and 6 per cent. of oxygen. It should be noted that these two groups show almost identical distribution in spite of the fact that one group could hold the breath longer than the other.

There were two aviators who fainted at 11.3 and 11.1 per cent. of oxygen. The first, who held his breath ninety-one seconds, was suffering from ethmoiditis and was not fit; the other who held his breath for fifty-nine seconds and reported breathlessness at moderate altitude was found to be stale by the neurologist.

Two other cases are of interest because of early failure in the rebreathing test. The first held his breath ninety-nine seconds but showed a circulatory failure at 10.7 per cent. oxygen. He was found to be physically fit by the clinician but had never flown higher than an altitude of 10,000 feet. The next man held his breath sixty-eight seconds and became inefficient at 10.3 per cent. of oxygen. He was a heavy smoker and complained of being tired after flights at more than moderate altitudes.

There were 12 men who managed to hold the breath for from one hundred to one hundred and twenty-eight seconds, and these,

with one exception, who reached 8.3 per cent., remained efficient to 8 or less per cent. of oxygen.

The correlation of breath-holding with the rate of oxygen consumption was only -0.03 ± 0.06 . An analysis of the comparison of these two conditions fails to bring out as close relationship as the ability to hold the breath and the percentage of oxygen reached.

If, as we believe, the rebreathing low-oxygen examination gives satisfactory evidence as to how well a man compensates to low oxygen and high altitudes, then our data indicate that the breath-holding test alone would not suffice as a means for grading men for altitude flights.

Vital Capacity and Low Oxygen. In the Royal Air Force all candidates with a vital capacity below 3000 c.c. are rejected and all below 3400 c.c. are viewed with suspicion. Should a person require a large volume of air per minute it is evident that he may find a large vital capacity useful. In this group of 128 men when seated the average volume of air breathed a minute was 6.7 liters, and when under the influence of a low oxygen of 7.6 per cent. it was 11 liters or there was an increase of 4.3 liters in the total lung ventilation each minute. The vast majority of men when breathing air that contains from 8.5 to 6 per cent. of oxygen inspire at each breath from 600 to 1250 c.c., while their normal volume per breath of normal atmospheric air is between 360 and 640 c.c.⁴ We have found a few men when under the influence of 7 or 6 per cent. oxygen who breathed 2000 to 2400 c.c. of air per breath. It is obvious that a man of small chest might be limited to rapid rather than deep breathing in order to secure sufficient ventilation of the lungs when at altitudes comparable to such oxygen tensions as these.

Among the 128 men the vital capacity of the chest averaged 4330 c.c., the smallest was 3090 c.c. and the largest 6620 c.c. The coefficient of correlation between vital capacity and compensation to a gradually decreasing supply of oxygen was exceedingly small, only -0.06 ± 0.06 . This suggests that vital capacity when taken alone is almost a negligible factor in the process of making the compensations necessary to supply the oxygen needed by the tissues during exposure to a decrease in oxygen that is comparable to ascending in altitude at the rate of approximately 1000 feet per minute.

There were 5 men among our group of 128 who had a vital capacity of 3400 c.c. or less. They responded to the low oxygen altitude test as follows: (1) Capacity 3090 c.c. endured to 8.5 per cent. of oxygen; (2) 3180 c.c. reached 8 per cent.; (3) 3200 c.c. reached 8.9 per cent.; (4) with a capacity of 3380 c.c. went to 8.4 per cent. and (5) 3400 c.c. remained efficient to 7.6 per cent. of oxygen. These

⁴ Schneider: Jour. Am. Med. Assn., 1918, lxxi, 1386.

men reacted as well to oxygen want as many men of greater vital capacity. They did not, however, reach the very low oxygen of some of our cases. Two men with a vital capacity of only 3900 c.c. compensated well to 6 and 6.2 per cent. oxygen.

The 4 men who became inefficient early at 11.3, 11.1, 10.7 and 10.3 per cent. oxygen, percentages that are tolerated well by the vast majority of men, had vital capacities of 4680 c.c., 3900 c.c. 4800 c.c. and 3830 c.c. respectively.

The man who had the largest vital capacity, 6620 c.c., became completely inefficient at 9.4 per cent. oxygen and would have fainted had he not been restored to air immediately.

It appears from the data cited above that the vital capacity when taken alone does not give reliable evidence as to a subject's ability to respond to low oxygen and altitudes. Our experience unfortunately does not include men who at the same time had a small vital capacity and a limited ability to hold the breath.

The Expiratory Force in Relation to Low Oxygen. Unquestionably the expiratory force test is a measure of the power of the abdominal and other expiratory muscles. That the strength of these muscles should be of importance in making the necessary responses for providing oxygen from an atmosphere deficient in this gas does not appear a necessary or even likely correlation. Our data gave a coefficient of correlation for the relationship between the expiratory force and compensation to low oxygen of -0.11 ± 0.06 . This is slightly above the correlation between vital capacity and low oxygen and not equal to that between the power to hold the breath and low oxygen. All are too low to be significant.

The coefficient of correlation has been calculated for 120 cases for the relationship between expiratory force and the power to hold the breath and vital capacity. The correlation for expiratory force and the breath-hold was 0.48 ± 0.05 , which is a fairly high and quite significant coefficient of correlation. The correlation between expiratory force and vital capacity was 0.24 ± 0.06 , which presents a decidedly lesser degree of correlation, but which, nevertheless, is considerably higher than our correlations for these tests with the low oxygen compensation.

Among our group of cases subjected to the low oxygen altitude test there were three men who gave only 70 mm. in the expiratory force test. They compensated to low oxygen down to 8.4, 6.3 and 6 per cent. respectively. On the other hand the 4 men who made a poor showing in the low oxygen test, failing at 11.3, 11.1, 10.7 and 10.3 per cent. of oxygen, registered 140, 178, 88 and 110 mm. respectively in the expiratory force test. Not one of them was below 80 mm., the minimum for normal. These cases here cited are all exceptional, but they clearly show why the coefficient of correlation for expiratory force and low oxygen compensation is so decidedly low.

"Fatigue" Test. This is a form of breath-holding in which the subject by expiratory effort sustains a column of mercury at 40 mm. during the period that he holds his breath. It requires a considerable amount of effort, and therefore, for the majority of men, shortens the period that the breath can be held. Since the test is a modified breath-holding, it was to be expected, as was proved, that its coefficient of correlation with compensation to low oxygen, which was -0.12 ± 0.06 , would be about equal to that for the breath-holding test.

Our men in the "fatigue" test averaged 52.2 seconds. The highest record was ninety-seven seconds, made by a man who compensated down to 7.9 per cent. of oxygen. The minimum record of twenty-three seconds was made by a man who compensated well to an extremely low oxygen, 6 per cent.

Six men who reacted poorly to the rebreathing low oxygen test may be cited to further show the lack of correlation of these tests. They failed at the following percentages of oxygen: 11.3, 11.1, 10.7, 10.3, 10 and 9.9. Their respective "fatigue" tests were: 61, 36, 32, 63, 42 and 45 seconds.

The Extra Respiratory Reserve Factor. For 126 of our men the coefficient of correlation for this reserve factor and compensation to low oxygen was surprisingly low, only 0.025 ± 0.06 . According to Bazett⁵ a low figure for the reserve factor, under 30, indicates that the man is a good type for high altitude flying; such a man should therefore compensate well to low oxygen. Among our subjects there were many striking exceptions. One man with a reserve factor of 41 compensated to 5.7 per cent. oxygen, another with a factor of 40 reached 6.2 per cent. oxygen and a third with a factor of 45 remained efficient to 6.5 per cent. oxygen.

There were 52 of 126 cases who had an extra reserve factor of less than 30. These men compensated to low oxygen as follows: 17 to between 6 and 7 per cent., 24 to between 7 and 8 per cent., 6 to between 8 and 9 per cent., 4 to between 9 and 10 per cent. and one to only 11.3 per cent. oxygen. The average low oxygen reached by our 128 cases was 7.6 per cent. Of this group of 52, with a low figure for the extra reserve factor, 11 failed to reach 8 per cent. oxygen, and therefore could not be classed high in compensation to low oxygen and altitude.

It appears from the above data that any one of the five respiratory tests when taken alone does not give a reliable index as to how well a man may compensate to altitude and low oxygen.

In Table II are given the data for 7 cases of early failure in the rebreathing low oxygen test. It should be noted that two of these cases stand well in each of the respiratory tests and that the others only fail to fulfill the English standards in one or two of the tests,

the extra reserve factor and the "fatigue" test. The combination of the respiratory tests does not appear to single out men incapable of compensating to low oxygen any better than did the individual tests.

TABLE II.

No.	Inefficient at oxygen, per cent.	Vital capacity, c.c.	Breath held, seconds.	Expiratory force, mm. Hg.	"Fatigue" test, seconds.	Extra reserve factor.
1. . . .	9.4.	6620	55	138	55	18.9
2. . . .	9.9	3950	60	122	45	32.8
3. . . .	10.0	4220	52	96	42	36.5
4. . . .	10.3	3830	68	110	63	35.0
5. . . .	10.7	4800	99	88	32	37.2
6. . . .	11.1	3900	59	178	36	33.5
7. . . .	11.3	4680	91	140	61	24.0

A Comparison of the Tests and Clinical Findings. Among the men considered in this paper there were 31 who were found to be below par by clinical departments of the laboratory. Each man was examined by an internist, neurologist, ophthalmologist and ear, nose and throat specialist. We shall now briefly show how these men responded to the several respiratory tests.

The Rebreathing Low Oxygen Examination as a Test of Physical Fitness. There were many incidents observed among aviators that seemed to indicate that the man who had "gone stale" was very sensitive to low oxygen and particularly liable to syncope when flying. In the laboratory we have seen men with temporary indispositions, such as may follow a bad cold, recent illness, lack of sleep, alcoholic excess, etc., do poorly in the rebreathing examination who at some other time when feeling fit had compensated very well. In view of these occasional findings the reactions of the 31 stale or ailing men was not what might have been expected. They compensated to low oxygen as follows: 11 to as low as between 5.5 and 7 per cent., 12 to between 7 and 8 per cent., 7 to between 8 and 9 per cent. and one to 9.9 per cent. oxygen. From this data it appears that among men who are physically below par some may react very well to the action of low oxygen, as judged by their physiologic and psychologic responses and efficiency.

The rebreathing low oxygen test was perfected to determine the ability of the human organism to respond to the decreasing oxygen tensions of high altitude. Some men compensate well, others inadequately and others not at all. The test should be employed for searching out those unfit for flying by reason of inability to respond to altitude, and also for approximating the altitudes safely tolerated. Physical fitness it appears must be measured by other tests.

Physical Fitness and the Simple Respiratory Test. The determinations for the 31 temporarily unfit men are tabulated below:

Breath-hold.			Expiratory force.		
30 to	39 seconds	= 1	80 to	89 mm.	= 1
40 to	49 seconds	= 0	90 to	99 mm.	= 1
50 to	59 seconds	= 4	100 to	109 mm.	= 3
60 to	69 seconds	= 9	110 to	119 mm.	= 10
70 to	79 seconds	= 5	120 to	129 mm.	= 5
80 to	89 seconds	= 8	130 to	139 mm.	= 3
90 to	99 seconds	= 2	140 to	149 mm.	= 2
100 to	109 seconds	= 1	150 to	159 mm.	= 0
110 to	119 seconds	= 1	160 to	169 mm.	= 1
			170 to	179 mm.	= 1
			180 to	189 mm.	= 4
Total		= 31	Total		= 31

Vital capacity.			"Fatigue" test.		
3000 to	3499 c.c.	= 1	20 to	29 seconds	= 1
3500 to	3999 c.c.	= 7	30 to	39 seconds	= 5
4000 to	4499 c.c.	= 11	40 to	49 seconds	= 7
4500 to	4999 c.c.	= 5	50 to	59 seconds	= 12
5000 to	5499 c.c.	= 6	60 to	69 seconds	= 2
5500 to	5999 c.c.	= 0	70 to	79 seconds	= 4
6000 to	6499 c.c.	= 1	80 to	89 seconds	= 0
Total		= 31	Total		= 31

Extra respiratory reserve factor.

10 to	19	= 3
20 to	29	= 11
30 to	39	= 5
40 to	49	= 3
50 to	59	= 3
60 to	69	= 0
70 to	79	= 2
Total		= 27

Only 1 of these unfit men held his breath less than forty-five seconds, the minimum for normal established in England; 1 had a vital capacity of 3180 c.c., which was below the minimum of 3400 c.c.; 6 held the breath in the "fatigue" test for less than the forty seconds, the minimum for normal, while 14 showed up unusually well in the extra reserve factor and only 8 made a very poor record, and not 1 was below the minimum normal allowed in the expiratory force test. There were 11 cases that did not fall below the minimum for normal in any one of these five respiratory tests while only 2 men fell below the minimum normal in three of the tests.

In the breath-hold 17 were above the average, 68 seconds; in the "fatigue" test 14 were above the average, fifty-two seconds; in the respiratory force 14 above 123 mm., the average, and 15 had a vital capacity greater than the average, 4330 c.c.

Our experience with these respiratory tests is similar to that of White⁶ in the U. S. Base Hospital No. 6 in France, in which he tried

⁶ AM. JOUR. MED. SC., 1920, clix, 866.

out the value of the breath-holding, vital capacity, expiratory force and the "fatigue" test on convalescent gassed cases. He concluded that they were tests of the stability of the nervous system, rather than of cardiac and pulmonary condition.

Birley⁷ working with English aviators at the front found that pilots and observers whose condition warranted their transfer to England for a rest preserved a comparatively high degree of physical fitness as judged by the tests. He believes that they afford valuable information in assessing temperament and susceptibility and reaction to shock. He found that they did not prove useful in searching out psychopaths, individuals, who never feel confident in the air and sooner or later reach the hospital with well developed anxiety neurosis.

Practice Effects. In order to determine the effects of practice and experience on the five respiratory tests 7 men were asked to repeat the tests every day for a week. The results obtained with 5 of the men are given in Table III. The data for the 2 men not recorded here show similar variations. It should be noted that the men followed their regular daily routine of living during the period and that no environmental conditions, habits of living or sickness were recorded that might account for the variations and improvement. Each man coöperated to the best of his ability, so we may conclude that the differences recorded are the results of practice and the fortunes of the details of coördination and position.

In breath-holding not a man held his breath the same length of time in any two trials. Each showed a considerable amount of variation. Six of the men improved the time of the hold with practice as much as eighteen to fifty-one seconds. Holding the breath requires will power, if a man determines to hold the breath until discomfort is profound, it can be done or he may give up with the first feeling of effort. Private Ha. by effort increased his power of holding the breath from thirty-one seconds, which is below the minimum for normal, to sixty-four seconds, which was within four seconds of the average for our group of 128 aviators.

In the "fatigue" test, which is also a breath-holding test, some skill is required in sustaining the column of mercury at 40 mm. and a proper set of the lips will appreciably ease the performance. All of our men also showed improvement with practice in this test. Sergeant L. R. increased his performance each day, so that on the fifth day he held sixty-three seconds longer than on the first day.

The expiratory force test practice effect shows improvement in five of the seven men. One subject, whose complete data are not here given, raised the mercury column to 132 mm. on the first day and to 218 mm. on the seventh day.

⁷ Report of the Air Medical Investigation Committee, London, 1918, No. 3, p. 25.
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TABLE III. PRACTICE EFFECT.

	1st day.	2d day.	3d day.	4th day.	5th day.	6th day.
SERG. L. R.						
Breath-hold in seconds	71	95	100	80	122	
Expiratory force in millimeters	50	68	72	68	160	
Vital capacity in cubic centimeters	5560	5400	5000	5200	5700	
"Fatigue" in seconds	30	50	55	64	93	
CORP. K.						
Breath-hold in seconds	65	67	63	58	76	
Expiratory force in millimeters	80	92	138	88	78	
Vital capacity in cubic centimeters	4300	4180	4100	4400	4100	
"Fatigue" in seconds	36	55	52	51	55	
PRIVATE I.						
Breath-hold in seconds	50	60	49	43	75	
Expiratory force, millimeters	120	140	180	116	160	
Vital capacity in cubic centimeters	4000	3900	3720	4000	3860	
"Fatigue" in seconds	..	46	55	40	63	
PRIVATE Ha.						
Breath-hold in seconds	31	57	64	59	56	
Expiratory force in millimeters	134	140	130	120	136	
Vital capacity in centimeters	4170	4190	4000	3970	4500	
"Fatigue" in seconds	40	48	65	54	49	
PRIVATE Hu.						
Breath-hold in seconds	62	65	85	81	75	82
Expiratory force in millimeters	60	54	70	96	94	104
Vital capacity in cubic centimeters	3700	3890	3650	3660	3760	3690
"Fatigue" in seconds	51	51	63	53	53	67

The data on vital capacity do not show that practice gives an increase in the record.

Conclusions and Summary. Certain criticisms may be offered against the simple respiratory tests. They require too much voluntary attention and hearty coöperation on the part of the patient. The results are not capable of physiologic interpretation unless they represent the best effort the patient can put into each test. Indifferent subject and listless observer both vitiate the results. If the patient wishes a vacation, knowing that a poor showing in the tests indicates fatigue and need of a rest, he can easily imitate the "all-in" man. The tests are in some respects psychologic, since if a man determines to hold his breath until

discomfort is pronounced it can be done or he may give up with the first feeling of effort.

To sustain the mercury column in the "fatigue" test requires some skill and a proper set of the lips may ease the performance so much that twenty and more seconds are added to the length of the hold. The expiratory force test, if well done, requires great effort and the height of the blow often depends upon the ability to co-ordinate the contraction of chest and abdominal muscles.

The coefficients of correlation for the power of breath-holding, vital capacity, "fatigue" test, expiratory force and extra respiratory reserve factor, with compensation to low oxygen, were found to be of such low value that the simple respiratory tests could not be accepted as aids in determining fitness for high altitude flying.

The degree of physical fitness it appears as shown by an examination of 31 temporarily unfit men cannot be measured either by the simple respiratory tests or by the low oxygen of the rebreathing test.

Seven men were able to improve their records in the respiratory tests by practice.

SACCULAR ANEURYSM OF THE DESCENDING THORACIC AORTA, WITH DIRECT RUPTURE INTO THE LOWER LOBE OF THE LEFT LUNG AND THE LEFT PLEURAL CAVITY:

THE REPORT OF A CASE AND REMARKS ON RUPTURE AND
HEMOPTYSIS IN AORTIC ANEURYSM.

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At this time when quantitative and functional studies are so much in vogue, one hesitates on first thought to present a morphologic study. Nevertheless, the writer is of the opinion that such studies still hold a definite and valuable place in clinical medicine. In spite of the fact that our viewpoint has been expanded to incorporate the newer ideas of functional pathology, the clinician must still depend in a large part upon a thorough knowledge of gross pathology for his interpretation of physical findings. With this idea in mind it appears that unusual and instructive cases should be conscientiously studied and recorded, notwithstanding the fact that some of the work will doubtless be a repetition of what has been done.

The medical literature of aneurysm in all its phases is already astonishingly extensive and varied, and associated with its scientific

development and collaboration are innumerable illustrious names in the annals of medicine.

The present paper was stimulated by a case which recently occurred in the Medical Service of the University of California Hospital, which the writer unfortunately did not see antemortem. The necropsy findings, however, directed my attention to the subject of aneurysm of the descending thoracic aorta, with special reference to rupture into pulmonary structures. The following report is interesting in the light of the necropsy findings:

Case History. The patient, J. S., a white man, aged fifty years, American, was admitted to the University of California Hospital on March 29, 1920, at 7 P.M. and died on March 31, 1920, at 2.30 P.M. On admission his temperature was 38.4° C., respiration 36 and pulse 104. He complained of "cough and weakness," which was of four years' duration, and of a pain in the left lower chest.

Family History. Father died at sixty-eight of unknown cause; mother died at seventy-two of old age; two brothers killed; one sister died at twenty-seven during childbirth. Patient married at twenty-seven and was divorced four years later; no children.

Past History. Born in Colorado and lived in California from thirty to fifty. He has been employed as a miner and steel-miller.

Diseases. Does not remember having childhood diseases. Influenza at twenty-five and again at forty-eight. He had pneumonia at thirty-four, and Neisser infection without known complications at eighteen and forty; lues denied.

Accidents. He is said to have fractured skull at twenty-three.

Habits. He had used alcohol steadily all his adult life and had been a heavy smoker.

Present Illness. Four years ago the patient had a sharp pain in the right lower chest, which increased in intensity during coughing and deep breathing. Since then he states that he catches cold very readily and has had a chronic cough; he has been below par most of the time. About four months ago the patient had a severe cold, with a chill and fever, but was not sick enough to be in bed. Since then he has improved slightly but has not felt as well as formerly. Four days ago patient was again seized with chills and fever, and yesterday morning on arising he felt a sharp pain in the lower left chest; this pain was more marked on deep breathing and coughing and was relieved by lying on the affected side. Although he has had some cough for the last four years, this has been more severe during the last three months. Recently he has had considerable sputum, mostly of the colorless, stringy, mucous variety but never blood-tinged. There is no history of hemoptysis nor night-sweats. His best weight is 180 pounds; average weight 170 pounds; present weight 158 pounds. He has had some shortness of breath off and on for the last three years, but this has been especially noticeable during the last three months.

Physical Examination: Well-developed and nourished man, lying on the left side, coughing frequently and expectorating a thin sputum mixed with a small amount of light greenish, mucopurulent material. Patient complains of sharp pain in the left lower chest. Head, ears and nose are negative. Eyes: Bilateral pterygium on the corneæ; pupils regular and equal and reacting actively to light and accommodation; extra-ocular movements well performed;



Specimen removed at autopsy; posterior view. *a*, descending thoracic aorta; *b*, opening into the aneurysmal sac; *c*, posterior wall of the aneurysm; *d*, lower lobe of the left lung.

fundi normal. Mouth: The teeth are absent; tongue heavily coated, symmetrical and freely movable. Tonsils: Atrophic; pharynx is injected. Neck: Negative and the thyroid is not palpable. Chest: Conforms to the moderate pigeon-shaped variety. Right side is more prominent than the left anteriorly. In the upper thoracic region the spine is slightly deviated to the right. The right supraclavicular area is depressed. There is a

marked impairment of the percussion note in the left axilla which extends forward, fusing with the relative cardiac dulness and extending posteriorly to the left base. Over this area tactile fremitus is absent. There is a friction rub high in the left axilla. Anteriorly below the left clavicle the breath sounds are harsh and loud. Grocco's triangle of dulness is made out at the right base along the spine. Heart: P. M. I. is best heard at the fifth rib in the left parasternal line; the R. C. D. is displaced markedly to the right; the right border of the R. C. D. is made out 5.5 cm. to the right of the mid-sternal line in the fifth right interspace. There is a loud, blowing systolic murmur heard best at the aortic area. This murmur can be heard as far up as the first interspace and as low down as the third interspace on the right side. There is no diastolic shock over the sternum to be made out. The rhythm is regular; the rate is 108 per minute. Pulse shows good tension, rapid rise and fall, and the vessel wall is not palpable. Blood-pressure is $\frac{110}{80}$. Abdomen has normal contour and is rather resistant to deep palpation; no definite tenderness nor masses are made out. Genitalia are negative. Deep reflexes are equal and active throughout. The mental state is apparently normal. Blood examination: R. B. C., 3,800,000; W. B. C., 13,000; differential count (100 cells): P. M. N., 81; S. M., 14; L. M., 5; P. M. E., 0; P. M. B., 0. Urine examination: Sp. gr., 1.026; cloudy; acid; albumin, F. P. T.; sugar, 0; sediment, many urates and a few pus cells, but no casts. Impression: Tuberculous pleurisy, with effusion at the left base and displacement of the heart to the right.

March 31, 1920, at 9 A.M. Patient complaining of pain in the left side especially on cough. Side strapped with adhesive. Patient coughed considerably.

March 31. At 2.30 P.M. adhesive strapping was removed in preparation for thoracentesis. Patient continued coughing in paroxysms. He expectorated a small amount of a foamy, mucoid sputum and complained of pain in the left lower chest. Suddenly he began bringing up a small amount of blood, at the same time he became very restless and sat up straight in bed, and after four or five gasping spells he became unconscious and cyanotic, and respiration ceased rather sharply. The whole amount of blood expectorated did not exceed 30 or 40 c.c. The heart-beat was audible for a moment or two after respiration ceased.

Wassermann (on blood serum postmortem) was triple plus.

Fluoroscopic and roentgen-ray examinations had not been done because the patient was too ill to move.

Clinical impression as to the cause of death: Massive pulmonary hemorrhage into a bronchus in a case of ulcerative pulmonary tuberculosis.

Postmortem Record of the Pathologic Laboratory. A. 20.59, University of California, performed by Dr. G. Y. Rusk, autopsy one hour after death.

Anatomic Diagnosis. Aneurysm of the aorta, with rupture into the left lower lobe and into the left chest cavity; syphilitic aortitis; dislocation of the heart to the right apex in the midline; chronic local pleurisy about the aneurysm; pulmonary syphilis (?); chronic infarct in the spleen; acute anemia; chronic aortic valvulitis, with adhesions between the segments leading to slight stenosis.

Remains of a muscular, well-nourished male adult of normal stature. Rigor mortis absent. Body heat well retained. No superficial lymphadenopathies. The pupils are circular and equal. Moderate conjunctivitis is present. The left chest appears slightly fuller than the right.

On making the usual median incision the bodily fats are normally preserved and of normal color. The voluntary muscles are somewhat pale and the rib cartilages are somewhat more than normally calcified. On opening the left chest cavity there is a gush of blood-stained serum. The posterior surface of the sternum is negative. The left chest cavity contains an abundance of clotted blood and separated serum.

The heart is displaced to the right, so that the apex lies in the midline. The chest cavity is free from adhesions or fluid.

The right lung is voluminous and shows an average amount of pigmentation. It is hypercrepitant on palpation throughout. On section it is negative except for a moderate grade of diffuse emphysema.

The left lung, while somewhat compressed by the great amount of fluid in the pleural cavity, still is somewhat enlarged. The upper lobe is diffusely hypercrepitant, the lower lobe posteriorly superficially shows ragged point of rupture situated about one-third of the distance above the diaphragm on its posteromesial aspect. Adjacent to this, and extending to what subsequently proved to be an aneurysmal sac, is an area of diffuse opaque pleural thickening, but without adhesions. The tissues of the lower lobe, especially posteriorly, are suffused with hemorrhage which gradually diminishes in intensity toward the more anterior portions. The lung was removed together with the entire aorta, which will be described below. On section through the lower lobe there is found an area of irregular fibrosis extending in a wedge-shaped manner from near the root to the periphery through the center of the lower lobe. This area contains several patches of necrotic material and the process strongly suggests scarring associated with gummata.

The pericardial cavity contains about 30 c.c. of clear, fluid, serous transudate. The heart is of normal size considering the general development of the individual; it weighs 320 grams. The epicardial fat is normal. The relative size of the chambers appears normal. The endothelium of all the cavities, including the valves, except the aorta, appears normal. The myocardium is of normal thickness. The muscle is contracted. No areas of fibrosis were

observed. The aortic valve shows the right posterior segments to be adherent and the line of juncture thickened, pulled forward, separating the region of attachment of the segments for about 1 cm. from the aortic wall. On either side of this line of attachment there is a diffuse, gradual, lessened thickening of the adherent cusps, which extends to the region of the corpus on the posterior segment and throughout the whole of the right segment. This deformity appears to have led to a slight stenosis. The aorta just above the aortic cusps shows some irregular, soft, slightly yellowish superficial patches of atheroma, and in addition presents a number of areas, with irregular depressed, stellate creases of syphilitic aortitis. This condition of specific aortitis occurs with remarkable frequency throughout the whole length of the aorta. In the mid-thoracic region the left wall of the aorta presents a large opening, 8 x 10 cm., where it opens widely into an aneurysmal sac, approximately 8 cm. deep. The base of the aneurysm is formed by a thrombotic layer, which is supported on the thinned-out wall. The point of actual rupture into the bronchi is not determined until after fixation of the specimen.

The esophagus is normal, except that it was distinctly misplaced to the left by the aneurysmal dilatation.

The vertebra also as yet shows no destruction.

The spleen is moderately increased in size and somewhat softened. On section the pulp is pale, the Malpighian bodies are fairly numerous and only moderately distinct on the pale background. Corresponding to a small puckered scar in the cortex is a fibrous tissue thickening which extends about 3 mm. into the spleen, apparently the result of quite an old infarct.

The adrenals appear normal.

The kidneys appear normal.

The remainder of the urinogenital apparatus appears normal.

The pancreas shows a slight fibrosis in its distal half.

The liver appears normal except for slight palor.

The mesenteric and retroperitoneal lymph nodes are negative.

The mucosa of the gastro-intestinal tract appears normal.

Occurrence. Aneurysms of the descending thoracic aorta are the least common of all the aortic aneurysms, occurring only a little more than half as frequently as abdominal aneurysms. In 64 cases of aneurysms of the aorta among 2200 autopsies at the Johns Hopkins Hospital only 3 involved the descending thoracic aorta (Osler¹). Since the publication of Osler's monograph² on this subject, in 1903, little has been added to our clinical knowledge of descending thoracic aneurysm; however, since then much scientific advance has been made as to the causal relationship of syphilis to vascular disease and aneurysm formation, refinements in the roentgen-ray study have been outlined and numerous methods of therapy have been proposed and advocated.

Diagnostic Difficulties. Osler pointed out that in general there were three groups of descending thoracic aneurysm based on clinical observation and physical findings liable to present serious difficulties in the diagnosis, namely: (1) Cases which present symptoms only and no physical signs or the signs are not characteristic; (2) cases in which the symptoms and signs suggest malignant growth; (3) cases in which there are obscure and puzzling chest symptoms suggestive neither of aneurysm nor tumor (the above case falls into the third group).

The features which warrant classification of this case in the third group are based on the following data: (1) The comparative latency of all clinical symptoms except the history of pain of three months' duration in the left lower chest; (2) the cough was never characteristic or typical of thoracic aneurysm; (3) the striking yet misleading physical signs indicating fluid at the left base; (4) the absence of hemoptysis except as a terminal event.

Anatomical Considerations. Owing to the protected and deep position of the descending thoracic aorta, extending from the sixth to the twelfth thoracic vertebra, aneurysms of this portion are frequently silent. It will be recalled that the descending arch passes backward and downward to the left of the trachea, behind the root of the left lung, to the left anterior aspect of the thoracic vertebra. As it passes downward the esophagus and thoracic duct lie on its right. The left pleura and lung lie to the left and anteriorly. The descending arch of the aorta and the thoracic aorta below are held firmly in place by the intercostal branches which are given off from the aorta. In view of the existence of these special anatomic relations distinctive clinical manifestations may be produced which offer evidence of deep-seated thoracic disease. There are, in general, two large groups of structures which appear to be involved in aneurysms of the descending thoracic aorta, and when involved may give clinical evidence of intrathoracic disease. From the clinical standpoint the first group is the most common, although many special examples of involvement of structures in the second group are found.

Group I. 1. Spine, vertebra and spinal nerves. 2. Lung, pleura and bronchi. 3. Trachea and esophagus.

Group II. 1. Pericardium and heart. 2. Other great thoracic vessels, including pulmonary arteries, veins, etc. 3. Stomach. 4. Thoracic duct. 5. Diaphragm.

It is not my intention to review the symptoms and signs produced by encroachment upon or rupture into all of the above structures but rather to point out some of the facts of interest in regard to ruptured descending thoracic aneurysms into the pulmonary structures and particularly into the lungs.

Rupture of Aneurysms in General. It is a well-known fact, particularly to pathologists who perform large numbers of postmortem

examinations on medicolegal cases, that ruptured aneurysms stand high in the list of causes of sudden death. As long ago as 1895, *Draper*,³ in this country, published a paper entitled "Sudden Death by Rupture of Thoracic Aneurysm Previously Unrecognized," which emphasizes this point.

In reference to the cause of death from aneurysm, *Hare and Holder*⁴ state "that death occurs as a result either from rupture of the aneurysmal sac, from pressure of the sac upon important nerves and bloodvessels or from secondary changes which take place in these tissues and in other vital organs as a direct or indirect result of such pressure." *Arnold*⁵ made a study of the cause of death in aneurysms of the aorta which do not rupture. He found in a large series of aortic aneurysms of all types 110 of the descending aorta, and of these 15 per cent. were unruptured at death, whereas 66 per cent. were found ruptured. From his statistics it also appears that descending aortic aneurysms are slightly more liable to rupture than those in other portions of the aorta.

Oswald Browne's figures indicate definitely that the most common termination of aneurysms of the descending thoracic aorta is rupture into the left pleural cavity. In his series of 17 cases in which 14 ruptured, 7 instances of rupture into the left pleural cavity occurred. The incidence of rupture at other points was as follows: Right pleural cavity, 2 cases; left bronchus, 1 case; esophagus, 3 cases; subserous tissue, 1 case.

*Wilson*⁶ collected from the literature 75 cases of descending thoracic aneurysm, 53 of which had ruptured. In these ruptured cases he found that 13 cases had ruptured into the left pleura, 1 into the right pleura, 6 into the left lung, 16 into the left bronchus, 2 into the trachea, 2 into the pericardium and 9 into the esophagus. It was stated that in 2 instances rupture had occurred into the thoracic cavity, in 1 instance into the abdominal cavity, and once into the neck. In the remaining 22 cases rupture did not occur. Erosion of the vertebræ occurred in 26 instances, whereas an external tumor was encountered in only 6 of the 75 cases. In this series the clinical diagnosis was missed in 50 per cent. of the cases. In *Osler*'s series of 14 cases, rupture into the pleura occurred 3 times, whereas in *Wooley*'s⁷ recent series of 9 ruptured aneurysms of all types 2 ruptured into the left pleural cavity. The foregoing figures emphasize the marked tendency that aneurysms of the descending thoracic aorta have for rupturing into the pulmonary structures, and particularly into the left pleural cavity.

Hemoptysis. *Clarke*,⁸ in 1905, reported a remarkable case of thoracic aneurysm which had come under his observation. The case was unusual in that the patient had a series of 16 copious hemorrhages, and in a period of seven and a half weeks lost a total of fourteen pints of blood before exitus occurred with hemorrhage. In the last moments of life during the fatal hemorrhage the physical

signs of fluid at the right base were made out. The autopsy revealed a saccular aneurysm of the ascending arch of the aorta projecting into and occupying a great portion of the upper lobe of the right lung, with rupture of the aneurysm into this lobe and extensive hemorrhage into the right pleural cavity. The striking feature presented by this case is the possibility of copious non-lethal hemorrhage in cases of thoracic aneurysm.

In the same paper Clarke refers to a case reported by Johnson⁹ which appears very similar to the case I report above. Johnson's patient had long-standing symptoms of chronic pleurisy, but no history of hemorrhage until the fatal one. Aneurysm was not suspected, but at autopsy one was found of the descending aorta involving the lower left lobe of the lung. The aneurysmal walls were only one-quarter inch thick, composed of fibrin, and the lung and pleura were indurated.

Clarke concludes from his study of aneurysms in reference to hemoptysis "that hemoptysis is a common fatal termination in thoracic aneurysm, a very large hemorrhage may occur in this disease, without causing death of the patient, and that occasionally a patient may have one or more large hemoptyses, but finally die from some other complication of the aneurysm. The point of bleeding may be from rupture into the trachea or bronchi and may be stopped by the opening being plugged with fibrin or it may occur from involvement of the lung tissue itself. In the latter case it is probable that the small bronchioles open into the wall of the sac, but are compressed by it, that they normally remain closed, or are covered with fibrin. On exertion of moving, either the fibrin shifts its position or the straining of the coughing opens the ends of the small bronchi and the blood leaks out. When the patient again becomes quiet, either naturally or by means of narcotics the original condition is resumed and bleeding is temporarily arrested."

The foregoing statement appears to be a fairly reasonable explanation of the intermittent nature of hemoptysis in some of these cases.

Hall¹⁰ in an able paper on the subject of intrathoracic aneurysm groups the mechanisms of pulmonary hemorrhage in these cases under three heads: (1) Direct hemorrhage, that is, when there is a leak from the aneurysmal sac into the air passages; (2) indirect hemorrhage, that is, when the hemorrhage is the result of pressure either on the air passages, the bloodvessels or the lung tissue itself; (3) hemorrhage secondary to cardiac disease with engorgement, of the pulmonary circulation.

Remarks on Other Symptoms—Pain, Cough and Dyspnea. In my case presented above pain played the conspicuous role in the symptomatology. Hewlett and Clarke¹¹ have pointed out in a small series of descending thoracic aneurysms that pain was the prominent symptom. They found it was usually of extraordinary severity,

constant, subject to nocturnal exacerbations and resistant to all forms of medication. In general, pain is of three kinds: (1) Anginal, (2) that due to pressure, and (3) neuralgic.

It is a well-known fact that aneurysm often produces the clinical picture of angina pectoris,¹² and, further, that obscure and deep-seated thoracic pains of all variations are sometimes produced by pressure of intrathoracic aneurysmal tumors. In the neuralgic type pain reaches its maximum intensity and persists when the aneurysmal sac erodes the spine.

The mechanism of pain in thoracic aneurysm has been explained in various ways. Increased tension of the walls of the aorta can of itself become a cause of pain by stretching of the delicate nerves which run in the walls of the aorta producing a neuritis. Oliver¹³ states that digitalis administered in suspected cases often augments pain in the chest, since by improving the force of contraction of the left ventricle and by constricting the peripheral arteries it raises arterial tension. Other factors in the production of pain include, of course, that caused by pressure on adjacent structures and the coexisting inflammation.

Cough and dyspnea are practically always constant features of involvement of the aortic arch, but are less constant in aneurysm of the descending portion of the aorta. In Osler's 14 cases these symptoms were present in 10 instances. Bronchorrhea and bronchiectasis result at times from pressure on the main bronchus.

Summary. A case of descending thoracic aneurysm is presented which had ruptured directly into the left lower lobe and left pleural cavity. The physical signs were misleading and the clinical diagnosis was incorrect. It is probable that if a roentgen-ray study had been possible it would have aided materially in determining the true nature of the pathologic process. Rupture into pulmonary structures of descending thoracic aneurysms is one of the most frequent occurrences, particularly rupture into the left pleural cavity, less commonly into both lung and pleural cavity. Hemoptysis must be regarded as a symptom of thoracic aneurysm as well as a symptom of other thoracic disease, such as tuberculosis, mitral stenosis and other mediastinal tumors. It may be frequent and persistent before a fatal hemorrhage occurs.

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SILVER SALVARSAN IN THE TREATMENT OF SYPHILIS.*

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THROUGH the courtesy of Ehrlich's distinguished pupil and successor, Professor Kolle, early in November, 1919, Colonel Earl H. Bruns, chief surgeon, A. F. in G., received 1000 ampoules of silver salvarsan from the George Speyer Haus Laboratories, Frankfurt, Germany. Colonel Bruns turned this preparation over to Major Robert W. Kerr, Medical Corps, the Commanding Officer of the Base Hospital (now Station Hospital), A. F. in G., Coblenz, Germany, with instructions concerning its use which he had obtained personally from Professor Kolle. The first results seemed favorable and its further use was decided upon. Additional

* Weichbrodt, Knauer, Seeli-Bonn and Gennerich: *Ztschr. f. Aerztliche Fortbildung*, Georg Speyer Haus, Frankfurt.

supplies of this preparation were obtained through medical department procurement.

Since that time over 800 patients have been treated with silver salvarsan and mercury, more than 6000 injections having been given at the Base Hospital and Convalescent Hospital by or under the direction of the following officers: Majors Carter and Flynn; Captains Kimbrough, Raycroft and Moore; Lieutenants Cowen, Thomas, Blackburn, Bourbon and myself. The laboratory work in connection with the Venereal Clinic has been done by Major Gentzkow, Lieutenant McNeil and Lieutenant Elmendorf.

Composition and Description of Silver Salvarsan. Kolle¹ states that silver salvarsan contains 22.4 per cent. arsenic and 14.1 per cent. silver. Bauer² says that the silver in silver salvarsan is not present in the oxide or colloid form, but in a complex combination that may be considered half colloids, on the boundary between colloids and crystalloids.

He advances the theory, based on different experiments, that these semicolloids act as colloids in the system. He states that in silver salvarsan, neosalvarsan and old salvarsan the relative chemotherapeutic coefficient is silver salvarsan 1 to 25, neosalvarsan 1 to 10, old salvarsan 1 to 10. He further states that the arsenic component is materially decreased in silver salvarsan owing to the combination with the antisyphilitic silver component. His diffusion experiments make it seem probable that silver salvarsan is hydrolized in the body and set free as true colloids. A single dose of two-tenths (0.2) gm. of silver salvarsan contains 0.0254 silver and 0.043 of arsenic.

Silver salvarsan is prepared in the Ehrlich Laboratories at Frankfurt and the powder is placed in ampoules in the following doses: One-tenth (0.1) gm., fifteen hundredths (0.15) gm., two-tenths (0.2) gm., three-tenths (0.3) gm. The powder is grayish black and in solution takes on an ichthyol brown color.

Characteristics of Spoiled Silver Salvarsan. Silver salvarsan in the original ampoules keeps for an unlimited time so long as it is not damaged. Small cracks in the glass permitting the entrance of air cause silver salvarsan to become decomposed and thereby made poisonous. The decomposition is not so easily discernible in looking at an ampoule of the silver salvarsan while in powder form as when placed in a solution.

If the silver salvarsan has deteriorated the powder is darker in color and does not change to an ichthyol brown color when placed in solution, but takes on an opalescence of pronounced cloudiness, or it floats around on the surface of the water in black particles in which the undissolved silver salvarsan is recognized by the naked eye when the solution is held to the light.

Silver Salvarsan as a Spirocheticide. Kolle and Ritz³ state that silver salvarsan is to be considered a true combined preparation

containing two chemotherapeutically effective components, silver having a catalytic effect on the salvarsan molecule. They further state that it has been experimentally proved that arsenobenzol is a direct spirocheticide, because of anchoring of the arsenic in the spirochetic plasma. Many experiments, especially those showing the slow disappearance of the spirochetæ after the administration of this drug, incline to the opinion that silver acts as a restricting agent on the multiplication of spirochetæ. The action of the silver in silver salvarsan is successful in preventing an increase of spirochetæ because of the specific affinity of the salvarsan to the spirochetæ, the silver with the whole molecule of the silver salvarsan is anchored fast to the spirochetæ of the syphilitic tissues. For this reason the combination of the silver with the salvarsan is of special chemical therapeutic value. The silver salvarsan acts also on the spirochetæ within the syphilitic tissue as a combination remedy in the sense that this term was used by Ehrlich.

In a series of experiments they have shown that in rabbits the curative dose of the metal silver, or its salts, is one-hundredth (0.01) gm. to two-hundredths (0.02) gm. per kilogram of the rabbit's weight, the toxic dose for rabbits being six-hundredths (0.06) gm. to seven-hundredths (0.07) gm. The spirochetæ disappear slowly but surely from the infected rabbit. The hard chancre softens and finally disappears. Not only does colloidal silver but also organic and inorganic silver salts combined with albumin influence the manifestation of syphilis and the spirochetæ. The effect on the spirochetæ and its manifestations is slower with all silver salts than with arsenobenzol, but the former can be given in larger doses with less toxic effect. Spirochetæ disappear more slowly with colloidal silver than with non-colloidal compounds. The primary manifestations of syphilis in experimental animals disappear in from three to five weeks after therapeutic healing doses of silver compounds. Animal experimentation finds silver salvarsan twice as effective as salvarsan (606) and three times as effective as neosalvarsan (914). Kolle further states that silver salvarsan is old salvarsan in active form plus silver and that 0.25 silver salvarsan equals 0.4 old salvarsan.

Technic of Administration of Silver Salvarsan. Bruhns and Lowenberg⁴ use one-tenth (0.1) gm. of silver salvarsan dissolved in 20 c.c. of freshly distilled sterilized water; in the larger doses 30 to 40 c.c. of freshly distilled sterilized water.

Kerl⁵ uses 6 c.c. of freshly distilled water to every one-tenth (0.1) gm. of silver salvarsan. Delbanco and Zimmern⁶ make a solution with from 10 to 20 c.c. according to quantity of preparation. Lenzmann⁷ uses 20 to 40 c.c.; four-tenths (0.4) per cent. solution of sodium chloride. Schoenfeld and Birnbaum⁸ prefer 60 to 80 c.c. of normal sodium chloride (C. P.) solution. Kolle¹ recom-

mends 10 c.c. of distilled water to each one-tenth (0.1) gm. Dreyfus⁹ states that we should use only redistilled sterilized water from the Jena glass apparatus, avoiding the use of any metal that would come in contact with the solution except the platinum needle.

Kerl⁵ prefers a modified Arzt Schramek syringe. Lenzmann⁷ uses a Lieberg syringe. Birnbaum⁸ uses the Schreibus glass syringe. Kolle¹ suggests Wechselmann's apparatus.

Practically all the above-mentioned authorities emphasize the importance of giving the solution very slowly. Bruhns and Lowenberg⁴ state that the least time required for each injection should be at least two minutes. Kolle¹ calls particular attention to the irritating effect of silver salvarsan on the tissues and states that caution should be used so that injury to the inner wall of the vein does not occur and that great care is used in seeing that the needle is in the vein properly before administering the solution.

The technic used at the Station Hospital and Convalescent Hospital is as follows:

The water is distilled the day previous to its use. The distilled water is boiled on the day of the administration of the silver salvarsan. The water used is at room temperature. The silver salvarsan ampoules are immersed in 95 per cent. of alcohol, 20 c.c. of the sterilized distilled water are placed in a 60 c.c. medicine glass and the contents of the ampoule containing the silver salvarsan are dropped into the glass containing the distilled water. The silver salvarsan powder floats around on the surface of the water until it is completely dissolved, which takes approximately one minute. The solution now takes on an ichthyol brown color. The contents of the medicine glass are now drawn up into a 30 c.c. Luer syringe. Just prior to the insertion of the needle the operator dries same with a piece of sterile gauze in order to prevent the solution from coming into contact with the tissues. After the needle is introduced into the vein enough blood is withdrawn to fill the syringe. By this means we are positive of the needle being in the lumen of the vein, and, according to Kolle, the toxicity of silver salvarsan is immediately reduced by the addition of albumin or serum. The injection of the solution is made slowly, requiring approximately one minute. The needle is withdrawn quickly and the operator raises the patient's arm and uses marked pressure at the site of the injection in order to prevent extravasation of the fluid back into the tissues.

Dosage. Galewsky¹¹ considers small doses of silver salvarsan necessary in the treatment of syphilis. He commences it with five-hundredths (0.05) gm. for anemic women, otherwise one-tenth (0.1) gm.; increases the dose every four or five days to a final maximum dose of three-tenths (0.3) gm. to men and twenty-five-hundredths (0.25) gm. for women. Total given by him to

men in the course of treatment is 1.8 gm. and for women 1.5 gm. He ordinarily gives eight to fifteen injections of silver salvarsan in the first course of treatment for primary seronegative syphilis and four to six injections in after-treatment. In order to avoid what he terms spirochetæ fever in virulent secondary stage of syphilis, he gives a first dose of five-hundredths (0.05) gm. and second dose of fifteen-hundredths (0.15) gm.

Dreyfus⁹ states that no fixed total dose has been found as yet. He has given as high as 3 or 4 gms. to a patient in from six to ten weeks without after-effects.

Schoenfeld and Birnbaum⁸ state that they use for the first two or three doses for men one-tenth (0.1) to two-tenths (0.2) gm., and for women one-tenth (0.1) gm. to fifteen-hundredths (0.15) gm. For the next five or six doses in strong men they give three-tenths (0.3) gm. to thirty-five hundredths (0.35) gm. and for strong women two-tenths (0.2) gm. to twenty-five-hundredths (0.25) gm. They follow this treatment with three or four doses at six-day intervals, giving men twenty-five-hundredths (0.25) gm. and women two-tenths (0.2) gm. They state that the average total dose of 2.5 to 2.75 gm. for men and 2 gm. to 2.5 gm. for women should be given in ten to twelve injections.

Bruhns and Lowenberg⁴ give the following course of treatment: Twelve injections of silver salvarsan with three or four days' interval. For the first dose they give one-tenth (0.1) gm. followed by five doses of two-tenths (0.2) gm. and this is followed by six doses of twenty-five-hundredths (0.25) gm.

Kerl⁶ administers one-tenth (0.1) gm. and two-tenths (0.2) gm. of silver salvarsan on two succeeding days, and after an eight-day interval repeats the treatment until he obtains a negative Wassermann reaction. Later, because of the slow response of Wassermann reaction, he gave one-tenth (0.1) gm., two-tenths (0.2) gm.; two-tenths (0.2) gm. on three successive days and repeated after an eight-day interval.

Delbanco and Zimmern⁶ give on first dose five-hundredths (0.05) gm. or one-tenth (0.1) gm. Second dose, one-tenth (0.1) gm. and the next six to ten injections a dosage of two-tenths (0.2) gm. or twenty-five hundredths (0.25) gm. They gave their injections with an interval of from three to five days. They state that silver salvarsan may be given daily without bad results. Boas and Kissmeyer¹² gave only four injections in each treatment with a dosage of fifteen-hundredths (0.15) gm., twenty-hundredths (0.20) gm., and twenty-five-hundredths (0.25) gm. They state that when treatment has been going on for some time there should be a long interval between each dose, at least as much as eight or ten days.

Lenzmann⁷ gives at the first dose one-tenth (0.1) gm., and if no bad effects follow he then gives fifteen-hundredths (0.15) gm. on

the third day, on the sixth day two-tenths (0.2) gm., ninth day twenty-five-hundredths (0.25) gm., then four injections of twenty-five-hundredths (0.25) gm. a week apart, and on the following week a dose of three-tenths (0.3) gm. He further states in seronegative primary syphilis five to six injections are sufficient, while in seropositive primary syphilis it requires seven to ten injections, according to the duration of the positive reaction. He states that fresh secondary syphilis up to two or two and a half months' duration requires only one treatment of ten to twelve injections if the serum reaction turns negative four weeks after taking up treatment. Where this was not the case the patient with secondary syphilis received a second treatment six weeks after the first, consisting of eight to ten injections at five-day intervals.

Rille and Frühwald¹³ give in single doses from two-tenths (0.2) gm. to four-tenths (0.4) gm. of silver salvarsan at intervals of from three to seven days, giving in all six to eight injections.

Kolle¹⁴ states that we must try to make the therapy so effective in the nine to eighteen injections, intervals from two to five days, that in perhaps 90 per cent. or more of the primary or early secondary cases we may expect complete sterilization. He advises beginning the treatment with one or two injections of one-tenth (0.1) gm. and increasing the dosage to two-tenths (0.2) gm. for women, with twenty-five-hundredths (0.25) gm. for men as a maximum dose, with an interval of four days. He says that we should never give more than 2 gm. of silver salvarsan in a month.

Major Kerr appointed a Board of Medical Officers consisting of Major H. P. Carter, Captains Kimbrough and Raycroft to investigate and recommend a treatment for the cure of syphilis with silver salvarsan. This Board recommended the following treatment:

An interval of seven days between each dose in each course of treatment.

Treatment to consist of four courses of silver salvarsan and gray oil.

In the first course of treatment the first dose to be fifteen-hundredths (0.15) gm. of silver salvarsan.

Second dose to be two-tenths (0.2) gm. of silver salvarsan.

And each of the remaining five doses of the first course to be three-tenths (0.3) gm. of silver salvarsan.

At the end of the first course of treatment a Wassermann blood test and then thirty days' rest.

In the second course of treatment three-tenths (0.3) gm. silver salvarsan for each dose, with seven-day intervals, then two and a half months' rest. Course to consist of seven doses.

The third course same as the second with ninety days' rest.

The fourth course same as second or third course.

In conjunction with and at the same time of each injection of

silver salvarsan give eight-hundredths (0.08) gm. gray oil, intramuscularly.

A Wassermann blood test was recommended after each course and a spinal fluid examination after the second course. During the second year of the disease perform every three months a Wassermann blood test and lumbar puncture with a complete serological examination of the spinal fluid. If at any time the Wassermann becomes positive treatment will be renewed. If at the end of the twenty-fourth month the Wassermann blood test and spinal fluid are negative the case is considered cured. This treatment was later somewhat modified by making an interval of four days between injections during the first course.

Primary Syphilis. Hoffman¹⁵ states that with one complete intensive course of treatment with mercury and salvarsan in primary syphilis we get a complete cure. Hoffmann, Neisser and Scholz¹⁵ claim a successful abortive cure of syphilis should be attained in from 80 to 100 per cent. of all cases, *provided the patient presents himself for treatment in the prepositive Wassermann period.* Fabry¹⁶ states that it is generally admitted now that in primary lues sterilization is obtained prior to the positive Wassermann period in 100 per cent. of all cases. Galewsky¹⁵ says that in all cases of early syphilis showing a positive dark field and negative Wassermann they continued to show a negative Wassermann throughout their treatment with silver salvarsan and during one year of observation following this.

It is believed we have reached the point where we should differentiate between primary and secondary syphilis by the Wassermann, and consider syphilis with primary lesions, primary syphilis, until Wassermann is positive, and then call it secondary syphilis. One should be extremely cautious in stating that a cure has been attained in any stage of syphilis, and observation of a patient, both from a clinical and serological standpoint, for a period of many years, appears to be essential before drawing any definite conclusion. To tell a patient that even in early syphilis he will be cured may give him a false security that in the end may do him an injustice as well as others. It would seem a better plan to tell the patient that some authors claim a cure, but that a cure is not at all certain. However, this much is certain, as a rule, syphilis, like tuberculosis, can be controlled if the patient follows instructions.

In a study of our syphilitic registers there were found 133 early cases where a diagnosis was made by a dark-field examination. These cases were divided into periods of from one to five, five to ten, ten to fifteen, fifteen to twenty, twenty to twenty-five, twenty-five to thirty and over thirty days, in which, according to patient's statement, he had noticed the primary lesion. The cases in question have been under treatment anywhere from four to ten months.

The following table shows those cases which have always had a negative Wassermann and those which at some time during treatment the Wassermann became plus minus, plus or double plus:

No. of cases.	Days lesion existed.	Always negative.	Became plus minus, single plus or double plus while under treatment.	Approximate percentage always negative.	Approximate percentage run plus minus, single plus or double plus.
27 . .	1 to 5	22	5	81	18
43 . .	6 to 10	29	14	63	32
17 . .	11 to 15	13	4	76	23
7 . .	16 to 20	3	4	42	57
6 . .	21 to 25	4	2	66	33
8 . .	25 to 30	3	5	34	62
25 . .	over 30	9	16	36	64
133		83	50	62	37

In the above small number of tabulated cases, all of which were diagnosed by a dark-field examination, 83 ran a negative Wassermann throughout their treatment, and 50 cases became plus minus, single plus or double plus during treatment. *In all the cases in this series which gave other than a negative Wassermann, such result was obtained a few days after beginning treatment, and this would lead one to believe that the case when starting treatment was on the verge of, or actually in, the secondary stage.* It must also be understood that the information regarding the time the primary lesion had been observed was necessarily obtained from the patient, many of whom stated that the lesion was about the size of a lead pencil when first noticed. Sometimes the information given by the patient was *not dependable* because his statement might be what he deemed best for his individual interest, having in mind the disciplinary action necessary by existing orders in case he failed to take the prophylactic treatment required at the time of exposure. Upon questioning many of these patients about the duration of the primary lesion, explaining the reason such information was desired and assuring them the truth would not lead to disciplinary measures, I found in many cases the soldier had noticed the primary lesion much longer than stated in his original questionnaire. Unfortunately, at the time the re-investigation was made with reference to the duration of the local lesion, in most of the cases where the table shows a primary lesion existed anywhere between one and twenty days and Wassermann became plus minus, plus or double plus, the soldier had left the American forces in Germany.

It is held that *if* the period of the primary lesion could be definitely stated in the above tabulated cases, where the lesion existed less than fifteen days they would always run a negative Wassermann. It will be of interest to follow this series of cases many years in order to determine if there has been an apparent abortive cure of

sypilis. Certainly in this type of case only can we expect an abortive cure.

Wassermann Reaction in Secondary Syphilis. Hahn¹⁷ states that in cases of seropositive lues he usually obtains a provisionally permanent negative Wassermann with ten injections of silver salvarsan. In such cases he gives two injections a week, one of two-tenths (0.2) gm. and one of three-tenths (0.3) gm. Galewsky¹⁵ says that in a great number of cases of positive Wassermans after an injection of silver salvarsan the Wassermann remained negative and no symptoms showed up later. However, in these cases too short a time had elapsed to speak of permanent results. He also states there were isolated cases in which notwithstanding an application of salvarsan and mercury the Wassermann remained permanently positive. Sellei¹⁸ states that it is impossible to arrive at a definite conclusion from a survey of the cases so far treated with reference to the Wassermann. In two cases of secondary syphilis a reversion of the positive Wassermann was obtained within two or three weeks; however, he had a great number of cases where the Wassermann did not become negative until five or six weeks had passed. Hahn¹⁹ states that after twelve injections of silver salvarsan the Wassermann was always negative in fresh cases, and nearly always negative in older cases. In those cases in which it was not negative six more injections of silver salvarsan were made without injury to the patient, and in some instances he went beyond that number, reaching twenty-four injections. Fabry¹⁶ states that the reversion of the Wassermann in several cases had not come up to his expectations. In one-half of the cases treated by Hoffmann¹⁵ with ten injections of silver salvarsan the Wassermann reaction remained positive. Kolle¹ is of the opinion that we should obtain a negative Wassermann after twelve injections given as outlined by him under "Dosage" in this article, except in those isolated cases where there appeared to be a Wassermann-fast blood.

Knopf and Sinn,²⁰ in a series of 30 cases, 14 of which were treated with silver salvarsan alone and 16 with silver salvarsan and mercury, obtained the following results:

THE WASSERMANN BECAME NEGATIVE.

Without Hg, after silver salvarsan, gm.	Cases.	With Hg, after silver salvarsan, gm.	Cases.
0.8	1	0.8	7
1.2	3	1.2	4
1.6	6	1.6	1
1.8	2	2.4	1

The Wassermann remained positive twice without mercury and three times with mercury.

Müller³⁷ obtained the following serologic results in a series of 73 cases, using silver salvarsan alone:

Blood Wassermann after silver salvarsan.	L.I. 27	L.II. Manifest: 27	L.II. Latent 13	L.III. 5	L. Hereditary 1
0.6	8	4	4	1	—
0.9	5	2	—	—	—
1.2	6	7	5	—	—
1.5	5	4	—	1	—
1.8	3	3	2	—	—
2.4	—	6	1	—	—
Total	27	26	13	2	0
Remained plus, p. c.	0	1	0	3	1

At the Station Hospital and Convalescent Hospital in a series of 61 cases of secondary syphilis manifested by a double plus Wassermann and clinical evidence of the disease in the secondary stage, the following negative Wassermann reactions were obtained after each dose of the first or second course of treatment:

FIRST COURSE OF TREATMENT.

No. of cases.	Doses of silver salvarsan.	Doses of novo-arseno- benzol.	Doses of gray oil.	Gave a negative Wassermann.
2	1	—	1	2
2	2	—	2	2
6	3	—	3	6
9	4	—	4	9
11	5	—	5	11
7	6	—	6	7
10	7	—	7	10
1	1	6	7	1
2	1	6	7	2
—	—	—	—	—
50				50

SECOND COURSE OF TREATMENT.

3	1	—	1	3
2	2	—	2	2
1	4	—	4	1
2	6	—	6	2
1	—	4	4	1
1	—	5	5	1
1	—	6	6	1
—	—	—	—	—
11				11

Our present schedule of treatment provides a rest of one month between first and second course of treatment. A summary relative to Wassermanns in this series of 61 cases may be tabulated as follows: 55 cases received silver salvarsan and gray oil of mercury; 47 of these cases gave a negative Wassermann in the first course, which consisted of seven treatments. The remainder (8 cases) gave a negative Wassermann in second course of seven treatments.

Approximately 83 per cent. gave a negative Wassermann at end of first course, and the remaining 17 per cent. gave a negative Wassermann at the end of second course. Six cases received sometime during their treatment silver salvarsan, novo-arseno-benzol, and gray oil of mercury, three gave a negative Wassermann in first course of treatment and three gave a negative Wassermann in second course of treatment. The number of cases in this series is, of course, too small for any final conclusions; however, it would appear that silver salvarsan has a slight advantage over novo-arseno-benzol relative to reversing the Wassermann.

Our syphilitic registers show 516 patients have completed the first, second or third course of treatment, approximately 70 per cent. of these cases gave a negative Wassermann after first course of treatment, 25 per cent. gave a negative Wassermann after second course of treatment and 5 per cent. gave a negative Wassermann after third course of treatment. In other words the selected cases in a series of 61 with manifestations of secondary syphilis give a higher percentage of negative Wassermanns than these 516 cases. This may possibly be explained by the fact that in our series of 516 cases there are many who received a portion of their treatment with novo-arseno-benzol, others did not take treatment regularly, and still others probably had a latent secondary or tertiary syphilis.

Silver Salvarsan with or without Mercury. Galewsky¹¹ states that a Wassermann is negative sooner with silver salvarsan than neo-salvarsan, he further prophesies that there will be no more relapses into premature tertiary or premature neurosyphilis. He considers silver salvarsan the best remedy discovered to date, and as a result of two years' experience he prefers straight silver salvarsan to the combination of mercury and salvarsan. He thinks there are fewer after-effects than in any other salvarsan preparation tried.

Bruhns and Lowenberg⁴ state that silver salvarsan often works quicker than mercury salvarsan combination.

Hauck²¹ believes that the addition of mercury is unnecessary in giving silver salvarsan, he says that owing to the toxic effect it paves the way to salvarsan poisoning.

Nolten²² states that mercury is superfluous when using silver salvarsan.

Gennerich²³ states that the addition of mercury is unnecessary in giving silver salvarsan. He further states that in seropositive and secondary lues the Wassermann turns negative somewhat sooner with silver salvarsan than with other salvarsan preparations, even in combination with mercury. He recommends mercury only in cases where a third treatment is necessary because of the long time since infection. He says it can be used between the silver salvarsan treatments because it prevents the spirochetæ from recuperating.

Fabry²⁴ states that one must be extremely careful with mercury and silver salvarsan in combination. He believes you should begin with silver salvarsan and not follow too closely with the mercury.

Von Notthaft²⁵ thinks that treatment with silver salvarsan and mercury at the same time is a mistake, owing to the toxic effect of mercury on the liver and kidneys. Wechseltmann, Pinkus, Scholtz and von Notthaft have given up the use of mercury.

Boas and Kissmeyer¹² use mercury and silver salvarsan in combination. They state that mercury may be superfluous but it does no harm.

Lenz²⁶ states that he can only support in an approving manner the favorable results reported of silver salvarsan.

Kreibich²⁷ says that given the same proportion of arsenic, silver salvarsan is superior to old salvarsan, in which connection the inferior toxicity of the former permits a higher proportionate dosage.

Hahn¹⁷ states that the effect of silver salvarsan on syphilis is excellent; he has good results in all stages of syphilis. He had quite a number of patients who did not yield to other treatment but in whom after the administration of silver salvarsan the Wassermann became negative and remained so. He states that in seropositive lues with an average of ten injections of silver salvarsan he was able to obtain a permanent negative Wassermann.

Goldberger²⁸ states that considering the inferior toxicity of silver salvarsan compared with old salvarsan, and its higher efficiency compared with neosalvarsan, it makes a valuable addition to antisyphilitic remedies. He thinks a combination with mercury appears to be the best treatment.

Sellei¹⁸ states that silver salvarsan operates in a very energetic manner and after a very short time the symptoms completely disappear. He believes the use of silver salvarsan particularly indicated where there is a nephritis present.

Clinical Effects of Silver Salvarsan and Mercury. Kreibich²⁷ states that the same rapid and intensive effect is obtained on the spirochetæ with silver salvarsan as with old salvarsan (606).

Galewsky¹¹ states that within twenty-four to twenty-eight hours after an injection of silver salvarsan the spirochetæ are often not to be found in the local lesion.

Bruhns and Lowenberg⁴ state that the exanthemata disappear remarkably quickly; the running papules dry up one day following the injection and soon heal.

Lenzmann⁷ states that there was a decided influence on the spirochetæ four hours after a dose of one-tenth (0.1) gm. of silver salvarsan, within twelve hours practically no living spirochetæ could be found.

Major Gentzkow and Lieutenant McNeil, in the Laboratory

Service at the Station Hospital, did not find living spirochetæ in the initial lesion twenty-four hours after an injection of silver salvarsan. Lieutenant Elmendorf, of the Convalescent Hospital, states that actively mobile spirochetæ have been found as long as twenty-one hours after an injection of silver salvarsan fifteen hundredths (0.15) gm. plus eight-hundredths (0.08) gr. of gray oil, and that inactive spirochetes were found in the local lesion as long as twenty-six hours after an injection of silver salvarsan and gray oil. The number of spirochetæ present in preparations made after an injection of silver salvarsan and gray oil were invariably greatly reduced. No organisms were found forty-eight hours after the time of injection of silver salvarsan.

The effect of silver salvarsan on all grades of syphilis is favorable. The local manifestations appear to clear up as rapidly as they did under the older salvarsan preparations. There is a decided change in the initial lesion after the first treatment, indurations pass off quickly, glands are reduced in size, exanthemata pale down and the mucous patches and condylomata heal rapidly. The best apparent results obtained by silver salvarsan, as in all cases of salvarsan preparations, were in those showing the ordinary clinical signs of secondary syphilis, with mucous patches in mouth and throat and exanthemata.

Immediate Effects Sometimes Seen after Silver Salvarsan. *Anaphylactoid Symptoms.* Swift (*Jour. Am. Med. Assn.*, 1912), after experimenting with guinea-pigs showed that a serum change took place after the first injection of salvarsan which led to the sensitizing of the animal.

J. Danepz, R.D.L. (*Academie de Science*, 1916) is of opinion that the after-effects of arsenobenzol compounds, alarming in many patients, are caused by a precipitation within the capillaries. According to him this precipitation is caused by the reaction of an antibody with the next injected arsenobenzol. He recommends giving oversensitive patients small preparatory doses.

Kolle, Schlossberger and Leupold,²⁹ in their experiments with mice showed that intravenous injections of small doses of salvarsan gave certain protection against an 'absolutely deadly' dose twenty-four hours later. Many investigators place the after-effects of salvarsan preparations in the category of anaphylaxis, and insofar as the first injections are concerned, as parallel to primary serum poisoning. For this reason the after-effects manifested soon after the beginning of intravenous salvarsan injections are frequently called anaphylactoid.

Galewsky,¹⁵ speaking of so-called angioneurotocal symptoms, states that these symptoms were noticeable immediately after the first injection with some of the patients; with others they only became manifest after subsequent injections, so that it can only be a question of anaphylactoid manifestations after repeated intravenous injections of silver salvarsan. He states the symptoms

were chiefly noticeable in persons strongly alcoholic, or in patients suffering from heart affections.

Hahn¹⁹ says that the anaphylactoid symptom-complex turns up immediately after injection, he rarely came across it and it never became an embarrassing form except in the case of patients where an affection of the meninges was to be presumed.

Friedlaender³⁰ described cases suggesting to him the idea of anaphylaxis, wherein patients showed a few clonic twitches which were rapidly transformed into a shaking tremor of the whole body, cyanosis and weak pulse. In his opinion in these cases it is a question of Herxheimer reaction and the term anaphylaxis has only been used to account for the clinical similarity of the symptoms with genuine anaphylactoid manifestations.

From the most recent investigations by Schmalt, Giessen and Sachs³⁰ the presumption appears justified that anaphylaxis is not a chemical reaction of the albuminous substance but a process due to physical causes. These authors, apparently quite independently of one another, come to the same conclusion, viz.: that anaphylaxis can be produced by the incorporation of non-albuminous substances, as for instance carbohydrates, provided colloids only are concerned, but that the true anaphylactic effect immediately disappears if such solutions are first passed through a Berkefeld filter and the filtrate only is injected, or if the emulsion is considerably heated before injection so that the colloidal solutions are transformed into chemical solutions. They come to the conclusion that in intermittent silver salvarsan treatment the danger of anaphylactoid manifestations comes into question at the time of the first injection, and that for the repeated use of it it would be advisable to commence each fresh series with a small dose in order to first overcome the oversensitiveness.

Angioneurotic Symptoms. Lenzmann states that a strong concentration of silver salvarsan leads to angioneurotic symptoms.

Delbanco and Zimmern⁶ state that patients having a tendency to angioneurotic symptoms should be given injections very slowly.

Schoenfeld and Birnbaum⁸ speak of angioneurotic symptoms which are sometimes followed by collapse.

Kolle¹⁴ states that angioneurotical manifestations are, as a rule, due to the repeated injections of too concentrated doses of the remedy, and in most cases they can be avoided. He further states that in treating patients attention is called to the necessity of good nourishment and to the avoidance of excesses of any kind. By following these directions the angioneurotic symptom-complex can most certainly be avoided. But it should be pointed out that the said symptom-complex does not in any circumstances offer any apprehension, because so far no single case of death due to silver salvarsan has been recorded, in spite of more than 100,000 injections.

Hahn¹⁹ states that the 1-per-cent. solution as used by him renders it possible to prevent the cropping up of angioneurotic symptoms.

Goldberger²⁸ states that he never saw the so-called angioneurotic symptom-complex as described by Pinkus,²⁸ nor the vasomotor signs as were observed by Galewsky²⁸ and Sellei.

The angioneurotic symptoms as described by many authors are: vomiting, dizziness, pain in the back, edema of lips and face.

Spirochetæ Fever. In primary and secondary cases it is no uncommon occurrence to observe a rise of temperature after the first injection, which should be interpreted as spirochetæ fever; this does not constitute a contra-indication against a continuation of the treatment. If there is a higher rise of temperature after the second or third injection, or if the high temperature is continued over a longer period, further treatment must be interrupted for a certain time until the conditions of the patient have resumed their normal state.

Fabry³² states that spirochetæ fever is caused by the decrease in the number of spirochetæ, usually after injections with silver salvarsan in secondary lues. Should salvarsan anaphylaxis set in, increase the interval or decrease the dose.

Our experience has been that we get a reaction after the first dose of any arsenobenzol preparation in late primary or early secondary syphilis. We have always interpreted this as being caused by the spirocheticidal effect of any arsenobenzol preparation on the spirochetæ, thereby suddenly throwing a protein substance in the circulation and producing the so-called spirochetæ fever. This may be interpreted as angioneurotic symptom-complex, or anaphylactoid reaction. We have never seen a reaction following silver salvarsan that we considered alarming.

Neurorelapses. Ehrlich and Gennerich³⁴ have said that mono-recidives are caused by the local spreading of unsterilized spirochetæ. Kolle¹ thinks that we should never be alarmed over neurorelapses, he states there has never been a case of neurorecidive which was later reported as cerebrospinal syphilis. Kreiblich²⁷ and Sellei¹⁸ have not seen cases of nervous relapses after silver salvarsan. Galewsky¹¹ and Sinn³⁵ each report 1 case. In more than 800 cases our records do not show a case of neurorelapse.

Periphlebitis. This rarely occurs and is always due to faulty technic, the extravasation of the solution into the tissues at the site of injection, or trauma to intima of the vein. An abscess at site of injection has occurred only once to my knowledge in our complete series. In the out-patient clinic of this hospital there are given nearly three hundred injections on the morning of the day our out-patients are treated.

Effect on Later Manifestations of Syphilis. Weichbrodt, Knauer, Seoli-Bonn and Gennerich¹⁴ state that the spinal fluid is strongly influenced by silver salvarsan.

Dreyfus⁹ says that silver salvarsan can have after-effects more

frequently than neosalvarsan; however, he reports good results in syphilitic diseases of the nervous system. The best results were obtained in the early stage of the disease. He states that the subjective symptoms disappeared after a few injections and the objective symptoms in one or two weeks.

Kolle¹⁴ speaks of silver having been used for many years in the treatment of nervous diseases with apparently good results.

Hahn¹⁷ states that he obtained good results in cerebral syphilis and remarkable effects in tabes.

Galewsky¹⁵ also obtained good results with silver salvarsan in nervous syphilis.

Goldberger²⁸ is impressed with silver salvarsan and thinks that further investigations should be made with this drug.

In 2 cases in which Friedlaender³⁰ has used silver salvarsan he was led to believe that salvarsan or neosalvarsan is preferable to silver salvarsan in nervous syphilis.

Under the direction of Major Flynn, Captain Kimbrough has obtained the spinal fluid in 19 cases of patients under treatment in this hospital, after having finished their third course of treatment. The laboratory examination was made by Major Gentzkow, who reports the Wassermann negative in all these cases with the exception of 2, in which the spinal fluid gave a plus-minus reaction. The two last-mentioned cases had been treated with other arsenobenzol preparations during the first course of their treatment, and in addition they had not received their treatment regularly. In one of these cases the Wassermann was single-plus strong. The patient did not take treatment regularly, there was a lapse of six months between first and second course, and in the first course the patient was given novo-arsenobenzol rather than silver salvarsan. In the other case the Wassermann was plus-minus and the patient was given novo-arsenobenzol in the first course rather than silver salvarsan.

Captain Price, Chief of the Eye, Ear, Nose and Throat Service, has treated 8 cases of syphilitic iritis which were given silver salvarsan as outlined heretofore in this article. He states that he was greatly impressed with the results obtained by this drug. He wished to emphasize in particular one case which yielded surprisingly rapidly to treatment. The patient in question was almost entirely blind from interstitial keratitis on his admission to the hospital. He further states that the results obtained in this case with seven months' treatment with silver salvarsan were such as ordinarily he could not have expected before seventeen months.

Argyria. We have not been able to find any case of argyria reported in the literature, as the result of silver-salvarsan treatment. Our cases have not developed any such manifestations.

Poison after Administration of Silver Salvarsan. Foulerton³⁶ states it appears that the results characteristic of poisoning by

arsenobenzol compounds may be produced by the action of arsenic alone. But in view of the serious damage to the liver and kidney tissues in experimental poisoning with ortho-amido-phenol it is impossible to ignore the probability that the toxic action of the arsenobenzol drugs may be influenced to some extent by the benzene constituent.

So-called arsenic poisoning from arsenobenzol preparations may be classed as acute, subacute and chronic. In a series of more than 6000 injections of silver salvarsan in patients who are either still under treatment or who have been under treatment with silver salvarsan in conjunction with mercury, there have been only two cases of so-called arsenical poisoning which could be attributed to silver salvarsan. In all the other cases of poisoning at this hospital the patients received *ново-arsenobenzol*. One of these cases received three doses of silver salvarsan. First dose was fifteen-hundredths (0.15) gm. silver salvarsan, eight-hundredths (0.08) gr. gray oil. Second dose (six days later) two-tenths (0.2) gm. silver salvarsan, eight-hundredths (0.08) gr. gray oil. Third dose (four days later) three-tenths (0.03) gm. silver salvarsan, eight-hundredths (0.08) gr. gray oil. On the same day following the third dose of silver salvarsan and gray oil the patient suffered from headache, chills and dizziness, vomited twice and complained of pain in the epigastric region after the injection of silver salvarsan that day, three days later he developed sore-throat, diffuse erythema over the entire body, face edematous and red, a temperature of 101.4 and slight jaundice. The patient's urine was positive for albumin from the day following the second dose of silver salvarsan until fifteen days later. The other case received the first course of treatment. On the day following the last dose patient states the tips of his fingers and toes felt numb, skin became red in patches, which was quickly followed by a diffuse erythema, urine showed albumin and four days later early evidence of jaundice.

Albuminuria. Müller³⁷ states albumin in the urine was never noticed in his cases. Many authorities consider nephritis as a contra-indication to the administration of salvarsan, even in syphilitic nephritis. Sellei states that silver salvarsan had a favorable influence on the kidney in three cases where there was a nephritis in combination with the syphilis.

About 4 per cent. of our cases show albumin in their urine sometime during their course of treatment. They may be tabulated according to the number of doses of silver salvarsan and mercury as follows:

No. of cases.	No. of doses of silver salvarsan and mercury.	No. of cases.	No. of doses of silver salvarsan and mercury.
1	1	2	6
2	2	8	7
3	3	6	During 2d course.
4	4	3	During 3d course.
7	5		

In about one-half of the cases the albumin cleared up under further treatment and as would be expected these cases were those who showed albumin in the early part of the treatment. On the contrary, in those cases in which the albumin appeared during the latter part of first course or later, there was a tendency for the albumin to persist until further treatment was discontinued.

The confusing factor in cases showing albumin in their urine while under treatment for syphilis is the fact that we may be dealing with a transient or toxic albuminuria, from various causes, *i. e.*, syphilis, mercury, any arsenobenzol preparation or the various organic or infectious diseases.

In view the fact that many writers in using silver salvarsan alone do not speak of an albuminuria, it would indicate that in some of our cases in which this condition presented itself in the latter part of the disease it may have been due to mercury.

It is hoped that a report on albumin occurring during treatment may be made at a later date.

Summary. 1. Silver salvarsan is the strongest spirocheticide as well as being the least toxic of all arsenobenzol preparations, according to results obtained from animal experimentation, that has yet been introduced, and nothing has so far developed in its clinical application to contradict these observations.

2. Silver salvarsan deteriorates rapidly when exposed to the air, and this deterioration is recognized best when the silver salvarsan is placed in solution.

3. Technic of administration requires.

(a) Strict asepsis.

(b) Freshly distilled sterilized water in the proportion of 10 c.c. to each one-tenth (0.1) gm. of silver salvarsan.

(c) Silver salvarsan powder must be completely dissolved before administration.

(d) Proper precaution to prevent extravasation of the silver salvarsan solution into the surrounding tissues is essential.

(e) Slow administration, *i. e.*, not less than one minute.

4. If silver salvarsan is used alone probably the best treatment (based on the results reported in recent literature) is as follows:

Begin the treatment with one-tenth (0.1) gm. of silver salvarsan, increase dosage to two-tenths (0.2) gm. for women and twenty-five-hundredths (0.25) gm. for men as a maximum dose, with an interval of four days between doses, and never give more than 2 gm. in any one month.

5. The results obtained in primary syphilis on the Wassermann reaction are as good, if not better, than with any other arsenobenzol preparation used in combination with mercury.

6. The Wassermann reaction reversed to negative as rapidly in secondary syphilis with mercury and silver salvarsan as in any other arsenobenzol preparation with mercury.

7. Mercury should be given with silver salvarsan in the treatment of syphilis. Whether or not it should be given at the same time or following the silver salvarsan is another question. In military service it is desirable to give the two at the same time.

8. The effect of silver salvarsan on all clinical manifestations of syphilis is decidedly rapid, and appears at least as effective as that of any other arsenobenzol preparation.

9. Alarming effects of silver salvarsan were never seen in any of our cases.

10. Constant vigilance in the administration of all arsenobenzol preparations is essential. Particular attention should be given to patient's weight, a beginning erythema, functional kidney and liver tests.

11. Kolle, Ritz, Galewsky, Hauck and Gennerich appear to be of opinion that silver salvarsan is better than any other salvarsan preparation. Boas, Kissmeyer and Müller seem to think that silver salvarsan is on a par with salvarsan. Dreyfus, Kerl, Schoenfeld, Birnbaum, Bruhns, Lowenberg and Goldberger think that silver salvarsan is better than neosalvarsan. Hoffmann, Knopf, Scholtz and Sinn prefer salvarsan to silver salvarsan. Von Nothhaft says he obtains no better results from silver salvarsan than other salvarsan preparations. Friedlaender, Sellei and Hahn speak of very good results from silver salvarsan; Fabry says it might well be called upon to supplement or supplant neosalvarsan.

Conclusions. 1. Give mercury with silver salvarsan until it has been definitely proved that the mercury is unnecessary.

2. Energetic and intensive silver salvarsan and mercury treatment are indicated in early primary syphilis during the prepositive Wassermann period.

3. Silver salvarsan in so-called abortive treatment of syphilis is not so dangerous as other arsenobenzol preparations.

4. The literature on silver salvarsan and our own experience with this preparation, warrants the further continuation of its use.

5. An excellent field for the further study of these cases and the subject in general is now afforded at the Station and Convalescent Hospitals. It is hoped that the work is just begun, and that by a careful tabulation of the cases now on hand, and the careful observations noted in our syphilitic registers, by the teamwork of the various professional services and with the careful system of follow-up which it is expected to institute, this series of cases alone should in time enable us to draw definite conclusions as to the efficacy of this preparation.

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REVIEWS

SYPHILIS: DIAGNOSIS AND TREATMENT. By LOYD THOMPSON, Ph.B., M.D., Hot Springs, Arkansas. Second edition. Pp. 486; 81 engravings and 7 colored plates. Philadelphia, Lea & Febiger, 1920.

It is a pleasure to review the second edition of Thompson's book, now appearing after a lapse of three years, during which time its authority and value we feel has been thoroughly substantiated. There is not a great deal of change, but what is present is well chosen; for instance, the decline in value of the luetin test called for considerable retraction of its interpretation except in infants, the appreciation of the remote syphilitic manifestations allows of greater amplification in the chapters dealing with them, as is likewise true of the increasing use and dependency of the colloidal gold test, and we consider it wise, as the author has done, to establish the now almost universal custom of speaking of the *Spirocheta pallida* in preference to its other designations. The literature references are most complete and correct, while the illustrations, with few exceptions, are excellent and well chosen.

A. R.

SURGERY, ITS PRINCIPLES AND PRACTICE. By A. P. C. ASHHURST, A.B., M.D., F.A.C.S.; Associate in Surgery in the University of Pennsylvania; Surgeon to the Episcopal and to the Philadelphia Orthopedic Hospital. Second edition. Pp. 1202; 1129 illustrations and 14 colored plates. Philadelphia: Lea & Febiger, 1920.

THE first edition of this work was written in 1914. Since that time there has been much change in various treatments, conceptions and ideas many of which are due to the experience obtained as a result of the war. This the second edition brings the subject-matter up to date. Some of the old sections have been rewritten entirely. The branch of reconstructive surgery has been assembled into one place rather than being distributed throughout the book as in the first edition.

The chapter on gunshot wounds has been entirely rewritten, as

also have those sections dealing with shock, infected wounds, infections of the fingers and hand, hydrocephalus, carcinoma of the tongue, empyema, and surgery of the pancreas. Seven new colored plates and over one hundred new illustrations have been inserted. By means of judicious curtailing the new matter has all been added with only an increase of 60 pages in the size of the book.

Genito-urinary surgery, gynecology and orthopedics are discussed only so far as they concern the general surgeon. The specialties eye, ear, nose and throat are omitted.

The work is a most excellent one in most every respect. In fact in every respect but one and that is a fault of too much rather than too little in the way of choice and number of illustrations. Many of the illustrations of advanced conditions might better be replaced by earlier stages of the diseases, thus helping more in early diagnosis.

The work is good and the author is to be congratulated.

E. L. E.

NITROUS OXIDE-OXYGEN ANALGESIA AND ANESTHESIA IN NORMAL LABOR AND OPERATIVE OBSTETRICS. By F. H. McMECHAN, M.D., Editor. Pp. 97. Columbus, O.: Hahn & Adair Printing Company, 1920.

THIS distinctive monograph which has been prepared for the National Anesthesia Research Society by a number of anesthetists and obstetricians, who have acted as a Committee of Publication, gives a most comprehensive recapitulation of the modern theories of, ideas concerning, and methods of use of nitrous oxid as an analgesic and anesthetic agent in obstetrics.

P. F. W.

THE COLLECTED PAPERS OF THE MAYO CLINIC, ROCHESTER, MINN. Edited by MRS. M. H. MELLISH. Vol. XI, 1919. Pp. 1331; 490 illustrations. Philadelphia and London: W. B. Saunders Company, 1920.

VOLUME XI of the Collected Papers of the Mayo Clinic brings together the published work of fifty-four members of the staff for the year 1919 in an imposing volume of 1331 pages. The present volume follows the same physical make-up as its predecessors and contains many well executed illustrations. The one hundred and eleven papers composing the text are somewhat loosely grouped in nine sections, Alimentary Canal; Urogenital Organs; Heart; Blood; Skin and Syphilis; Head, Trunk and Extremities; Nerves; Technic and General Topics.

While the initial volume of this series was almost entirely of a surgical nature, the expansion and development of departments of correlated branches of medicine in this clinic with their consequent literary output, has given the volumes of recent years, and especially the present one, an extremely broad outlook. So one finds papers ranging from "Studies on the Electrocardiogram," "The Etiology of Poliomyelitis," "The Relation of Mouth Conditions to General Health" on through other branches of medicine with papers of a surgical nature composing the greater part of the text. Under the section on Technic one finds not only the "Technic of Gall-bladder Exposure" but also such a purely laboratory article as "The Use of Turpentine Resin in Turpentine as a Foam Breaker."

The splendid work of E. C. Kendall, Chief of the Section on Biochemistry of the Clinic, on thyroxin appears in three papers comprising about one hundred pages. Dr. William J. Mayo contributes five papers, and Dr. Charles H. Mayo, six papers, on surgical and general topics. Under the section on general topics the activities of the pathologic and laboratory services of the A. E. F. are described by Dr. L. B. Wilson, who played no small part in bringing these services to their high degree of efficiency. The volume closes with the addresses delivered at a memorial meeting in honor of Sir William Osler.

P. F. W.

THE SYMPATHETIC NERVOUS SYSTEM IN DISEASE. By W. LANGDON BROWN, M.A., M.D., F.R.C.P., Physician in Charge of Out-patients, St. Bartholomew's Hospital. Pp. 161, 9 illustrations. London: Henry Frowde, Oxford University Press, and Hodder & Stoughton, 1920.

THIS is an amplification of the Croonian Lectures for 1918 given by the author before the Royal College of Physicians of London. Originally appearing in part in the *Lancet*, they well deserve this presentation in expanded form. The book opens with a short but excellent account of the sympathetic and parasympathetic portions of the autonomic nervous system. In this the author has succeeded in giving a simple exposition by describing only the main points and by making many allusions to function. In Chapter II is treated, from a modern point of view, the pathologic physiology of the adrenals, thyroid and pituitary—all endocrine glands stimulated by the sympathetic system. Then follows the consideration of the influence of the sympathetic system and endocrine organs on glycosuria. As part of this there is a discussion of Allen's theory of diabetes, pituitary and other glycosurias and the polyglandular hypothesis. In the chapter on the sympathetic system and diseases of digestion are treated such topics as reflex dyspepsia,

enteralgia and hyperchlorhydria. Equally interesting are the discussions of the circulatory system and of vagotonia. From a consideration of the variety of subjects treated it will easily be seen what an important part the autonomic system plays in the life-processes of the individual, both in health and in disease; and the book gives an excellent presentation of the modern advances of our knowledge in this field.

W. H. F. A.

DIATHERMY IN MEDICAL AND SURGICAL PRACTICE. By CLAUDE SABERTON, M.D., Hon. Radiologist to the Harrowgate Infirmary and to the Royal Bath Hospital, Harrowgate; late Hon. Medical Officer to the X-ray and Electric Department, Royal Victoria and West Hants Hospital. Pp. 138; 33 illustrations. New York: Paul B. Hoeber, 1920.

PART I of this book is devoted to technic and deals with the production of high-frequency currents, diathermy apparatus, physical properties and physiologic effects of diathermic currents and methods of application. In this part of the book a lot of valuable information is condensed in a small space and set forth in such manner that it may be easily grasped by the student.

Part II is devoted to medical applications of diathermy. These applications cover a wide range of diseases, and one cannot help but think that the author is just a bit extravagant in his claims of almost universally good results in some of the nervous conditions and affections of the thorax.

A discussion of diathermy in surgery constitutes the third and best part of this little volume, the chapter on treatment of bladder tumors being especially good.

J. D. Z.

BACKWATERS OF LETHE (SOME ANESTHETIC NOTIONS). By G. A. H. BARTON, M.D., Anesthetist to the Hampstead General and Royal National Orthopedic Hospitals. Pp. 151; 11 illustrations. New York: Paul B. Hoeber, 1920.

IN a series of seven essays Doctor Barton offers the crystallized results of his twenty years' experience in anesthesia. The essays deal in an entirely unconventional and very personal style with the various anesthetic agents used, and detail the small practical points which he has found of value. He describes anesthesia as an art, developed since the former days when "chloroform killed some on the table, but ether killed more afterward in bed." The essay on

the use and abuse of alkaloids in anesthesia should be of interest to surgeons as well as anesthetists, while the closing essay "Shoals and Rapids" narrates his experiences with some of the more common dangers in anesthesia.

P. F. W.

A MANUAL OF PATHOLOGY. By GUTHRIE McCONNELL, M.D., Pathologist to the Cleveland City Hospital. Fourth edition. Pp. 611. Philadelphia: W. B. Saunders Company, 1920.

A GREAT deal of information is contained in this excellent little book. The author has displayed unusual ability in choosing the more important facts and presenting them clearly, briefly and accurately.

The text is divided into two parts: the first part embraces general pathology including postmortem technic, some laboratory technic and bacteriological methods and the second part covers special pathology. These subjects are arranged in the usual manner and the book should continue to prove quite useful not only for general reading and to those who wish to review the essentials of these subjects as in preparation for examinations, but as a handy laboratory manual.

J. A. K.

OCCUPATIONAL AFFECTIONS OF THE SKIN. By R. PROSSER WHITE, M.D. (EDIN.), M.R.C.S. (LOND.), Life Vice-President, Dermatologist, Senior Physician and Enthetic Officer, Royal Albert Edward Infirmary, Wigan; Vice-President, Association Factory Surgeons; Life Fellow, London Dermatologists' Society; Member, Manchester Medical and Dermatologists' Societies; Hon. Life Member, St. John Ambulance Association; Associate Editor, *Journal of Industrial Hygiene*, S.M.O. and Cadet Colonel, Church Lads' Brigade. Second edition. Pp. 360; 23 illustrations. New York: Paul B. Hoeber, 1920.

THE second edition of this excellent book, inaugurated by Dr. R. Prosser White, has been entirely rewritten, and has doubled in size. This increase has, undoubtedly, been necessitated by the new trades and many combinations of chemicals which are now in use, including the eruptions which were directly caused, and some of which have appeared, as an aftermath of the war. A comparison of the first and the present second edition show the enhanced value of the latter. The volume now contains eleven chapters, with the following titles: A circumspection; a conspectus; physical agents; acids, alkalies and some metallic salts; the dermatosis; industries; occupations; trades; synthetic dyes; dermatitis

venenata; zoetic dermatopathy. As a reference work it should be interesting to any one to read the present work carefully, as it will help tremendously in diagnosis, prevention and treatment. A considerable number of new photographs have been added, which also increase the value of the work. The references are many and will prove useful to those investigators desiring to write along these lines.

F. C. K.

THE ENDOCRINES. By SAMUEL WYLLIS BANDLER, M.D., F.A.C.S., Professor of Gynecology in the New York Post-Graduate School and Hospital. Pp. 486. Philadelphia and London: W. B. Saunders Company, 1920.

"THE influence and action of the endocrine glands are evidenced by somatic, mental and psychic changes." This constitutes the premises upon which the author proceeds to explain many symptoms and disturbances that are apparent to all practitioners in medicine, unexplained by definite physical and laboratory analysis.

Beginning at birth he develops the individual physically and mentally, the completeness and efficiency of the same depending on the harmony of the pluriglandular system; discussing at length, gynecologically, from puberty to the climacterium, including the disturbance of sterility, pregnancy, labor and placental glands.

He discusses each individual gland, hyper- or hypofunctionating—pineal, thymus, parathyroid, hypophysis, adrenals, ovaries, testis, including the mammary and placental gland. He quotes freely from authoritative research, blending logically acknowledged endocrine physical defects, thereby concluding that instinct, emotions, nervous defects, mental deficiency and criminality, neuroses, psychosis and phobia can be explained by faulty balance between the endocrines.

The anamnesis and symptoms are covered in detail, concluding with several clinics and numerous cases; practical from a standpoint of diagnosis, including the glandular therapy and results.

Gynecologically and neurologically the subject is practically and exhaustively treated equally advantageous to the general practitioner and the specialist.

The cardiocirculatory changes encountered in endocrine disorders might have been allotted more space likewise so lightly has he dealt with differential diagnosis, namely, thyrotoxicosis *versus* chronic pulmonary infection, etc.

A difficult subject masterfully handled, supported by the attitude, "I give you what I have found of value."

J. A. S.

REPORT OF THE SURGEON-GENERAL OF THE U. S. ARMY TO THE
SECRETARY OF WAR, 1920.

This report is the annual report covering the general activities of the medical department for the fiscal year ending June, 1920, and containing the statistics for the United States Army for the calendar year ending December 31, 1919.

Additional factors in this report compared to the previous years are statistics concerned with the demobilization of the war army and the restoration of the sick and injured and finally aiding in the building up of the new army and the recruiting of the medical department thereof and the medical department sections of the officers' reserve corps.

E. L. E.

SURGICAL CLINICS OF CHICAGO. Vol. IV, No. VI (December, 1920). Index number. Pp. 219; 57 illustrations, with complete index to Vol. IV. Philadelphia and London: W. B. Saunders Company.

This December number completes Vol. IV of the *Clinics*. It contains a very complete and satisfactory index to the volume, which volume has 1336 pages and 398 illustrations. This number contains nineteen separate articles by as many authors, all of whom are familiar to readers of the *Clinics*. It maintains the high standard set by the previous numbers.

From this date the *Clinics* cease to exist as the *Surgical Clinics of Chicago*, but don a new cloak and become the *Surgical Clinics of North America*. A distinctly attractive feature of this new and broader work is the plan to have each number, published every two months, devoted exclusively to the work at one great surgical center. The Philadelphia number appears in February, 1921.

E. L. E.

OPERATIVE SURGERY. By PROF. DR. VICTOR SCHMUDEN, Univ. of Halle, and ARTHUR TURNBULL, M.B., PH.B. (GLASGOW). Second edition. Pp. 350; 436 illustrations. New York: William Wood & Co., 1920.

This is a handbook for practitioners and students and has been remodelled to fit the latest ideas of what an operative surgery should be. Ligations which, in the past, were the important branch of surgery, have been relegated to a secondary position and more important operations are given precedence.

Only topographical anatomy and surgical technic are considered in these pages and the latter only so far as can be practised on the dead subject. The purpose of the book is to sum up and illustrate operative surgery for the beginner as well as the graduate. The book is made concise by omission of discussion of the various methods as to frequency, etc. Simple methods have been everywhere preferred to complicated ones and modern technic and the newer operations have supplanted those of time-honored usage.

The book is a good one of its kind, but, of course, is not a textbook of operative procedure in the living body. E. L. E.

PHYSIOLOGIC PRINCIPLES IN TREATMENT. By W. LANGDON BROWN, M.A., M.D. (CANTAB.), F.R.C.P., Physician with Charge of Out-patients, St. Bartholomew's Hospital; Physician to the Metropolitan Hospital, etc. Fourth Edition. Pp. 426. New York: William Wood & Co., 1920.

WE had the pleasure of reviewing the third edition of this work in 1914. Much has been learned during the intervening years concerning many points in physiology, and this much has been well woven into the fabric of the earlier edition to make this latest one even a better book than its predecessor. The same plan of subject treatment is carried out and the chapter headings remain unchanged. Brown calls well for his material upon the rich field which the English physiologic school supplies. We failed, however, to read something of Kendall's thyroxin and other interesting Cisatlantic contributions in recent years.

The chapters on diabetes and acid intoxications have received much revision. They are especially interesting because they call attention to the work of Graham, in St. Bartholomew's, on the fasting method of treating diabetes. Apparently quite independently Allen in this country, Graham in England, arrived at much the same conclusions concerning this therapeutic procedure. The war, however, prevented the publication of Graham's results in any sort of comprehensive form. Graham seems to advocate a short mitigated fast of forty-eight hours with a much more speedy addition of protein than Allen advises. Brown has had less experience with the Allen treatment, but feels that starvation to a glycosuria-free point may be more injurious to health than in the Graham forty-eight-hour method.

The chapter on irregular action of the heart remains untouched. The portion devoted to "the athletic heart" has, however, been abandoned for some lines on "the soldiers' heart" in the light of wartime experiences.

We like the book very much. It is helpful to the man who cares to apply newer physiologic principles to his clinical work. Brown has for a decade or more combined the practice of medicine in London with the teaching of physiology. The result has been the production of a splendid work with, of course, a decidedly English atmosphere.

T. G. S.

THE DETERMINATION OF HYDROGEN IONS. First Edition. By W. MANSFIELD CLARK, M.A., PH.D., Chemist, Research Laboratories of the Dairy Division, United States Department of Agriculture. Baltimore: Williams & Wilkins Company, 1920.

THE limitations of this book are contained in the title. It is a detailed exposition of the colorimetric and electrometric methods for determining hydrogen ion concentration and does not enter into a discussion of the relation of hydrogen ion concentration to biological and chemical processes. The first chapter contains a general mathematical discussion of the relation of acids and bases to hydrogen ion concentration. The pH scale, buffer action, and effect of dilution are elucidated. In the course of the next sixty pages the theory and procedure in applying the colorimetric method are discussed. A brief exposition of the theory of indicators is given and in addition to directions for preparing the buffer mixtures with which the author's name is associated those for the mixtures of Sørensen, Walpole and Palitsch are also given. The electrometric method (potentiometer method) is discussed to the extent of 106 pages. In addition to an adequate presentation of the mechanical features the theoretical aspects are reviewed with considerable clarity. While the superiority of the potentiometer method over the older compensation procedures is unquestioned, in view of the expense of the apparatus it would seem as though some mention might have been made of the simpler equipment which served Sørensen and others so well.

A bibliography of sixty pages concludes the book. The references are classified and one may find what work has been done in a particular field with great facility. Among the subjects in the classification are bacteriology, blood, catalysis, cerebrospinal fluid, comparative and general physiology, digestion, hemolysis, iso-electric points, serology and urine.

The book is written from a critical viewpoint so that one may get a good idea of the sources of error and deficiencies of the methods as well as some comprehension of the direction research is taking in the elucidation of the obscure though minor phases of the general subject.

R. L. S.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Lymphosarcoma, Lymphatic Leukemia, Leukosarcoma, Hodgkin's Disease.—WEBSTER(*Johns Hopkins Hosp. Bull.*, 1920, No. 358, xxxi, 458) calls attention to the confusion existing among pathologists as to the proper classification of these conditions. After the careful study of 123 cases falling into this group, all of which came to autopsy, he arrives at the following conclusions: "(1) It seems probable that lymphosarcoma, lymphatic leukemia and leukosarcoma are different manifestations of the same disease. (2) The term 'lymphadenosis, leukemic or aleukemic' would express this idea, and simplify the classification, until a definite etiological agent is found. (3) This disease is not a neoplasm, but a direct response on the part of the lymphocytes to a chemotactic influence exerted by the disease-causing agent. The presence of this substance in any tissue or organ produces there a local accumulation of lymphoid cells. (4) Diagnosis and prognosis of this disease in its early stage is difficult from the microscopical examination of a single gland because of its resemblance to certain types of benign lymphadenitis. (5) Evidence of ameboid activity on the part of the lymphocytes is indicative of a rapid, fatal course. (6) Hodgkin's disease, a distinct entity, may be diagnosed and accurately prognosed from the microscopic examination of a single gland."

Tuberculosis of the Spine Resembling Pyelitis.—FOSTER (*Jour. of Urol.*, 1920, No. 6, iv, 559) notes that occasionally disease of the spine, sufficient in extent to cause nerve injury with its resulting pain, does not cause impaired motility, and thus leads to a mistaken diagnosis. A case is reported in which the patient gave a history of unilateral pain suggesting pyelitis. Intermittent fever and pyuria were

present. Cystoscopic examination revealed pus coming from the kidney on the side of the pain. Examination of spine and radiograms negative. The diagnosis of pyelitis was made. Two months later kyphosis and signs of tuberculous disease of the vertebræ developed.

Dangers to Life Associated with Gall-stone Disease and Their Prevention.—TILTON (*New York Med. Jour.*, 1921, No. 1, cxiii, 4) considers the following as the chief dangers that threaten life: (1) Acute suppurative or gangrenous cholecystitis; (2) cholangitis; (3) malignant disease of the gall-bladder; (4) operation in delayed cases. Acute cholecystitis produces exquisite right hypochondriac pain, frequently radiating to the right shoulder. There is at times a chill. Hyperpyrexia occurs; sometimes vomiting. Examination reveals marked abdominal rigidity, and a mass caused by the distended gall-bladder and adherent omentum. Jaundice is usually absent. There is a leukocytosis with high polymorphonuclear count. The treatment advised in the severe cases is surgical, simple drainage being the operation of choice. Cholangitis implies common duct blockage with resulting infection. Jaundice is the most characteristic symptom and is often accompanied by chills, intermittent fever, sweats and prostration. The ultimate treatment is surgical. The choice of the time for operation is a question of surgical judgment. Operation is more hazardous at the height of the attack, yet if the symptoms persist for forty-eight hours and the patient's general condition is growing worse it offers the best chance for recovery. Simple drainage meets the vital indications. If the patient recovers from an attack under medical treatment he should not be allowed to run the risk of a recurrence. "One attack of jaundice associated with stones indicates operation in the absence of other factors that may contra-indicate operations in general." Malignancy of the gall-bladder is not a rare complication of gall-stones. Every chronic, thickened gall-bladder with stones has the possibility of malignant change, and should be removed. The history is that of repeated gall-stone attacks. When hepatic metastases are present the case is hopeless. Surgery may be successful if the growth is confined to the gall-bladder. Under the heading of the dangers of operation in the delayed cases, the author discusses the cases of gall-stone carriers from the standpoint of operative risk, noting the frequency with which one meets in them evidences of cardiac and renal disease. Attention is called to the fact that these delayed operations are usually more difficult and prolonged. These dangers can be avoided by operating in the early stages of the disease. The conclusion is reached that early operation in cholelithiasis is strongly indicated.

The Pulse-rate in Relation to Metabolism and Diagnosis.—(*Jour. Am. Med. Assn.*, 1921, lxxvi, 181). The fundamental work of Benedict and Murchhauser on the relationship between metabolism and pulse-rate in normal individuals is cited, as is the more recent work of Means and Aub, and Sturgis and Tompkins. The writer notes that discrepancies between pulse-rate and metabolism occur, but calls attention to the fact (Sturgis and Tompkins) that a pulse-rate at complete rest of below 90 a minute is seldom, and below 80 a minute is rarely associated with an increase in metabolism. This finding is of

much clinical importance in the recognition of the large group of nervous patients with symptoms suggesting hyperthyroidism, and in many instances of tachycardia not dependent upon thyroid disease.

Leukanemia.—SYMMERS (*Jour. Am. Med. Assn.*, 1921, lxxvi, 156) reports a case which clinically fell under this group-name, as originally described by Leube in 1900. The disorder is characterized by findings suggestive of both a primary anemia and myeloid leukemia, and is a rapidly progressive fatal malady. Stating that among hematologists the consensus of opinion is that the myeloblast is capable of differentiation into erythroblast on the one hand, and into granular leukocytes on the other, Symmers notes that in leukanemia the provocative agent seems to strike the bone-marrow with such intensity as to cause the appearance of both types of cells (erythroblastic and leukocytic) in the circulating blood. He summarizes as follows: "(1) Leukanemia is characterized clinically by an extremely rapid course and by changes in the blood, bone-marrow, spleen, liver and lymph nodes that partake both of the nature of pernicious anemia and myeloid leukemia, the causative agent acting on the hematogenic centers of the bone-marrow in such fashion as to produce marked numerical increase in those primitive cells which represent the precursors of both the erythroblasts and the granular leukocytes. The primitive cells in question are myeloblasts, as is shown by their morphology, and by the fact that they respond to the oxydase test. (2) Histogenetically, pernicious anemia, myelogenous leukemia and leukanemia are closely related conditions, and represent different quantitative responses on the part of the bone-marrow to regenerative stimuli acting on the same metrocyte, namely, the myeloblast. (3) Leukanemia is probably not an independent disease but one of a group of rapidly progressive derangements of the blood-forming tissues, due to infection."

Use of a High Fat Diet in the Treatment of Diabetes Mellitus.—NEWBURGH and MARSH (*Arch. Int. Med.*, 1920, xxvi, 647) report their studies of the use of high fat diet in the treatment of diabetes mellitus. Their observations are made on 73 cases of true diabetes mellitus. the majority of which were of the severest type. Despite this fact, they had succeeded in rendering and keeping their patients sugar-free up to the time of discharge from the hospital. The authors summarize their observations as follows: "Patients with severe diabetes, as a class, do not remain sugar-free on the usual high protein diet unless the total energy intake is kept so low that incapacity from starvation results. The only satisfactory diet is one which will keep the diabetic sugar-free, which will prevent the occurrence of serious acidosis, which will maintain nitrogen balance and which will make it possible for him to resume the ordinary activities of life. With these four points in mind, we studied the effect of a high fat, low protein, low carbohydrate diet in the treatment of diabetes. Our experience with this type of diet in the management of 73 cases has convinced us that it is capable of fulfilling these four specifications." The authors append examples of their diet.

SURGERY

UNDER THE CHARGE OF

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Surgical Treatment of Gastric and Duodenal Ulcer.—MAYO (*British Med. Jour.*, July 24, 1920, p. 103). If it is true that the majority of the causes of duodenal and gastric ulcer have an average duration of a number of years, many extending from twenty to thirty years, it is probable that there is an exaggerated idea of their danger to life. Few persons die from perforation, and few from hemorrhage—more, however, than die from surgical procedure. It is true that they suffer, are disabled, and should be relieved; and it is also probable that but a small percentage of the total number of ulcers are recognized or treated for the true condition. Gastric ulcers may give greater discomfort than duodenal ulcers, and, because of the danger of malignant degeneration, should be destroyed at the time of the operation unless this procedure would add unwarranted immediate risk, I believe patients who suffer from gastric ulcer should be told of this danger. In fact, the surgical treatment of ulcer is the best recognition of the value of medical treatment by permanently overcoming delay or obstruction and lowering the acidity with the patient's own alkalis.

Crucial Ligaments of the Knee-joint.—GROVES (*British Jour. of Surg.*, April, 1920) describes his operations for the repair of ruptured crucial ligaments of the knee-joint designed to restore their most important functions—namely, the checking of forward displacement of the tibia by the anterior, and of backward displacement by the posterior, ligament. The leg is encased in sterile stockingette through which a large U-shaped incision is made in front of the knee, its lowest part being just below the tubercle of the tibia, the inner limb running along the line of the inner hamstrings, and the outer one fingerbreadth on the outer side of the patella, the incision in the stockingette being fastened with clips to the skin edges. The tubercle of the tibia is chiselled off, the patella turned upward, and the interior of the joint exposed. In repairing the anterior ligament a strip of the iliotibial band, 8 inches long by $1\frac{1}{2}$ inches wide, is separated, retaining its original attachment to the head of the tibia. The external condyle is drilled, so that the inner end of the hole is far back in order that the new ligament may be as oblique as possible. The front of the tibia is then drilled, so that the inner end of the hole lies just in front of the tibial spine, its external orifice being over the most prominent part of the inner tuberosity of the tibia, the proximal ends of each canal being bevelled to make smooth funnel-shaped openings. With a strip of gauze as pilot the strip of iliotibial band is pulled taut through the femur and through

the head of the tibia, and, with the knee flexed, it is fixed by sutures and one ivory nail on the inner aspect of the internal condyle. After suturing the joint capsule the tubercle of the tibia is replaced and fixed by two bone or ivory nails. A similar procedure is adopted for repair of the posterior ligament with proximal strips from the semitendinosus and gracilis tendons. These are thrust through the inner part of the posterior ligament of the knee and pulled forward until their free ends hang out from the front of the joint, and they are then passed through a hole bored through the internal condyle opening as far forward as possible on the inner aspect of the intercondylar notch. After being pulled tight, with the knee fully extended, the free ends are turned downward and attached to the inner tuberosity of the tibia, and the joint closed. The knee is put up on a back splint, with daily massage and faradism to the quadriceps after three weeks. Six weeks after the operation a light plaster case is applied and patient allowed to walk, and a moulded case with lateral hinges is used later for three to six months.

Rib Grafting Operations for the Repair of Bone Defects and Their End-results.—ELOSSER (*Arch. of Surg.*, 1920, i, 428) says the rib graft is a feasible procedure. The viability of the grafts is great, even in the presence of suppuration. They are more liable to survive in the presence of infection than more massive grafts. They are rapidly absorbed. They hypertrophy slowly. They are prone to refracture (7 out of 22 cases). They are not so good as tibial grafts for the repair of large defects or when the graft is to be put under strain. They are particularly useful when no great demands are made on the strength of the bone, in repairing defects of the skull and in facial plastics. In such cases they should be used by preference. Of a series of 22 cases, 3 were failures, 13 were successes and 6 were partial successes.

The Relation of the Islets of Langerhans to Diabetes, with Special Reference to Cases of Pancreatic Lithiasis.—BARRON (*Surg., Gynec. and Obst.*, 1920, xxxi, 437) says pancreatic lithiasis is a very rare disease, which occurs mostly in males during the fourth decade. The obstruction of the pancreatic duct leads to an advanced atrophy of the pancreas accompanied more or less by fibrosis. The islets may remain intact even when the acini disappear completely. The islets are epithelial structures which are entirely independent of the acini and have no relation to or communication with the ducts. Changes in the islets, such as degeneration, necrosis and fibrosis—generally occur late in the disease, probably as a result of a superimposed secondary infection, consequent to a prolonged stasis in the ducts. In complete accord with the results obtained experimentally in animals, occlusion of the ducts by calculi in man does not result in diabetes mellitus unless there be actual injury to the islets. Cases of pancreatic lithiasis presenting symptoms of hyperglycemia and glycosuria reveal definite lesions of the islets at autopsy. The present study bears out the conclusions that the islets secrete a hormone directly into the lymph or blood streams (internal secretion), which has a controlling power over carbohydrate metabolism. Attempts at regeneration of injured pancreatic tissue

manifest themselves in a definite hyperplasia of the ducts. The principal clinical findings in cases of pancreatic lithiasis are colic-like epigastric pains often associated with temporary glycosuria, steatorrhea, alimentary glycosuria, incomplete digestion of meat fibers as revealed by the persistence of the nuclei in muscle fibers in the feces, and, occasionally, the presence of whitish or grayish pancreatic stones in the feces; the late stages are often accompanied by diabetes mellitus. Operations on the pancreatic duct are often successful. The danger of fat necrosis as a result of the escape of pancreatic fluid appears to be negligible.

Jaundice and its Surgical Significance.—MAYO (*Surg., Gynec. and Obstet.*, 1920, xxx, 545) says that jaundice as a symptom of disease may present a very serious problem in tracing its cause. Fifty per cent. of cases are due to common duct obstruction by a stone and 20 per cent. are due to infective or catarrhal jaundice without duct obstruction. Most of the latter cases occur in children and young persons. From 5 to 8 per cent. of cases of jaundice are due to serious infection of the gall-bladder, possibly gangrene, with or without stones. They are usually accompanied by a degree of pancreatitis. Fifteen per cent. of the cases seen are due to cancer, one-half of these from cancer of the liver, the other half from cancer of the pancreas or the gall-bladder and ducts. A short-circuiting operation relieves the patient often for months. The author has not had a permanent cure from transduodenal extirpation of the tumor of the ampulla. In 8 per cent. of the cases the jaundice was associated with ascites in cirrhosis. In cases of late operation for chronic jaundice the "white bile" which is found at operation and the failure of the power of biliary excretion to appear within a day or two following the operative drainage is a most unfavorable symptom. Long-continued jaundice shows the coagulation time is delayed and this may become serious. The best measure to decrease the coagulation time is the transfusion of acceptable human blood. This can be repeated just before and even after operation if necessary. If the gall-bladder shows marked evidence of disease it is removed. In the more serious infection, with degrees of gangrene, the procedure depends upon the condition of the patient. Another cause of jaundice is injury to the hepatic or common ducts at operation. Jaundice in which the head of the pancreas is enlarged and hard demands most careful consideration. This may be due to pancreatitis or carcinoma. The pancreas is involved secondarily to gall-bladder disease more frequently than was supposed. The gall-bladder may usually be looked upon as the primary focus and should be removed. The cases of obstruction associated with distention of the gall-bladder are best treated by attacking the gall-bladder after it has been emptied to the duodenum. In the cases of damage to the common duct following operation the ends should be sought and anastomosed, or if impossible the upper end is anastomosed to the duodenum or prepyloric region of the stomach. The passing of the bile into the stomach causes no distressing symptoms. In 1916, 1917 or 1918 anastomosis was done in 13 cases, 2 of which died. In 2460 cholecystectomies the mortality was 1.8 per cent. Of 337 cases in which cholecystectomy and choledochotomy were both done the mortality was 3.2 per cent.

THERAPEUTICS

UNDER THE CHARGE OF

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Treatment of Congenital Syphilis.—FORDYCE and ROSEN (*Jour. Am. Med. Assn.*, 1920, No. 21, vol. lxxv) report excellent results in congenital syphilis by the use of the following treatment: Mercuric chloride, gr. $\frac{1}{10}$ to $\frac{1}{8}$, in palmitin, intramuscularly with special needle (illustrated), and neoarsphenamin, gr. 0.075 to 0.2 in 3 to 5 c.c. of water, intramuscularly. This is given once a week for six to eight weeks followed by a rest period of from four to six weeks.

Etiology of Graves's Disease.—HOOVER (*Ohio State Med. Jour.*, October, 1920) states that the suspected etiology of Graves's disease rests on fanciful speculation and that there is no rational basis for specific treatment. The only evidence incriminating the thyroid is the improvement following irradiation and the superiority of this treatment over rest is so doubtful that judgment must be suspended. While hypothyroidism is definitely proved, hyper- and dysthyroidism are not. The histology and the combination of myxedema with Graves's signs cannot be adjusted to the theory of hyperthyroidism. Frequently cases are seen with the onset of Graves's disease accompanied by diminution in size of the thyroid. These are usually rapidly fatal. Thrills and murmurs over the gland are not diagnostic of activity. They may be due to pressure of the gland or bulbous enlargement, anemia, or dilated thyroid vessels. The hyperplased gland may exhaust itself and become necrotic or fibroid. This can be prevented by iodine, and Hoover advises as protective treatment the administration of 2 grains of potassium iodide or dessicated thyroid daily. When there is an increase in the symptoms following administration of thyroid, the product should be changed as this increase is due to some unknown ptomain. Graves's disease is always accompanied by globular enlargement of the heart. There is no decrease in the volume output. Stasis is never seen in early cases, no matter how rapid the pulse. In late cases, accompanied by hypothyroidism, myocardial and renal disease stasis may appear. The cardiac enlargement requires no treatment. The diagnosis of Graves's disease should be made apart from the basal metabolism, which should be used as an index of progress. The size of the heart and the pulse-rate are more accurate guides. Regarding treatment, Hoover advises rest, x-ray (though the value of this is *sub judice*) and states "I am unable to see any justification for the amputation of part of the thyroid gland as a direct treatment for Graves's disease."

PEDIATRICS

UNDER THE CHARGE OF

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Studies of the Heart in Nutritional Disturbances in Infancy.—McCULLOCH (*Am. Jour. Dis. Children*, December, 1920) studied a group of sixteen infants who showed moderate or severe degrees of athrepsia. Electrocardiograms were made on admission and at subsequent times when the evidence of a material change in the clinical condition was noted. In two of these infants alteration of cardiac mechanism was noted. This alteration was a delay in auriculoventricular conduction, and changes in the form of the Q R S complex. As an explanation of these disturbances the writer offers the suggestion that they were the result of alterations in the blood and body tissues in these infants. It is probable that the changes which had taken place in the blood resulted in a deficient supply of oxygen to the heart, with incomplete or delayed removal of metabolic products from the cardiac tissues. When improvement took place in the babies the alteration in cardiac mechanism disappeared. No evidence indicating heart failure was noted.

The Influence of Water-Soluble Vitamines on the Nutrition of Dogs.—KARR (*Proc. Soc. Exper. Biol. and Med.*, January, 1920) says that studies on a few species of animals have indicated that the water-soluble vitamine is of importance to nutrition during all stages of life and that prolonged absence of it from the diet will lead to a diseased condition. In his studies he has considered the role of the water-soluble vitamine in the nutrition of the dog. The animals were fed a diet devoid of water-soluble vitamine, consisting of lard, sucrose, inorganic salts and protein in the form of casein or wheat gluten. It furnished about 70 to 80 calories per kilogram of body weight. Such food mixtures were consumed readily by the dogs during a period of from three to nine weeks. After this time they refuse part or all of their food. Characteristic symptoms were developed by some. The ultimate failure to eat was always noted. Ingestion of as little as one gram of brewers' yeast, which had been previously dried, caused a quick recovery of the desire to eat. Five grams of the dried yeast will bring about the disappearance of the polyneuritic symptoms in eight to twelve hours and a quick recovery of the animal to its normal condition. The utilization of the protein nitrogen was not affected by the lack of water-soluble vitamine. The fat-soluble vitamine is of less importance than the water-soluble vitamine in the nutrition of dogs.

Fordyce's Disease as Pseudo-Koplik Spots and a Cause of Mistakes in the Diagnosis of Measles.—REGAN (*Am. Jour. Dis. Children*, June, 1920) defines Fordyce's disease as a chronic condition of the mucous membrane of the mouth and lips which is characterized by the presence of grayish or yellowish, scanty or abundant, discrete, aggravated and often coalescent milium-like bodies, occurring more especially on the

inside of the mouth laterally along the lines of the teeth as far back as the last molar. They occur somewhat less frequently on the vermilion or mucous membrane surface of the lips. It is among the conditions of the mouth, which may simulate Koplik's spots. They are especially to be mistaken for Koplik's spots when they exist in patients who develop German measles. The similarity of the clinical symptoms of the two diseases is further increased by the presence of the pseudo-Koplik spots. The resemblance between the two types of lesions may be rendered closer still because of the changes which the buccal mucosa undergoes in German measles which give it a deeper discoloration than normal. Fordyce's disease is quite frequently mistaken for early Koplik's spots in patients ill with various contagious diseases and exposed to measles, whose buccal mucosa is being examined daily for the appearance of Koplik's spots. The possibility of these pseudo-Koplik spots leading to errors in diagnosis when they are present in patients with suspicious-looking maculopapular eruptions from serum or antitoxin should be remembered. Well-marked and pronounced examples of Fordyce's disease are unusual in young children. Slightly marked cases are frequently seen in infancy, but the lesions are so small and often so situated so far back in the buccal mucous membrane, and is of so nearly the same color as the normal mucosa of the child, that it may be overlooked except where a careful search is being made for Koplik's spots.

Problem of Boarding-out, with an Attempted Solution.—CHAPIN (*Med. Rec.*, April, 24, 1920) has developed what is known as the Speedwell system. This has been on trial since 1902. Boarding-out is so systematized and regulated that the good points of this phase of the care of children has its best effects. This has been accomplished by developing what is known as a unit system of intensive boarding-out. A unit is a neighborhood that has been selected after a survey has been made to learn the general conditions of healthfulness and the number of good homes that may be available in the neighborhood. There is then inaugurated a constant oversight, especially as to diet and hygiene on the part of a salaried physician and nurse who are thoroughly familiar with the class of cases and competent to deal with them. The children are kept indefinitely until digestion and assimilation have improved sufficiently to result in a permanent increase in weight and strength. The work is continued during the whole year. In each neighborhood foster mothers are trained and they become fairly expert in the work. In comparing the results with institutional care to boarding-out it is found that both mortality and morbidity are less in the latter plan.

Measles: Brain Complications.—SKOOG (*Jour. Am. Med. Assn.*, June 19, 1920) reports two cases. He says that the literature indicates that the brain complications and sequelæ of measles occur much more frequently in children than in adults, and also occur much oftener during the convalescence than during the febrile or exanthem stage. He groups the brain complications and sequelæ under three headings: (1) The first group includes a certain small number of cases in which the relationship of the measles is merely incidental. The onset of the brain symptoms may be several weeks to several months after measles.

In such cases the bearing of the measles infection to the sequela may be questioned. (2) The second group includes the secondary infections due to various organisms. The bacteria may be delivered to the central nervous system by the blood stream. The mode of invasion in most instances is undoubtedly through the cribiform plate from the nasopharyngeal cavities. A great many more cases of meningitis follow measles, compared to all of the other complicating disorders of the central nervous system. (3) The third group is a less certain one, owing to the fact that the exact etiology of measles is as yet undetermined. Clinical studies of the disease lead us to believe that the blood stream is teeming with the virus. Accordingly the vascular channels of the meninges and the brain may readily become involved. Some of the brain complications first manifested during the eruptive stage, or the early convalescent period may be caused directly by the virus of measles.

Transfer of So-called Normal Antibodies.—REYMANN (*Jour. Immunol.*, May, 1920), by examining the transmission of agglutinins, normally occurring in the blood, from mother to offspring in goats, has been able to prove in only one case of fourteen examined that these agglutinins recurred. In all the other cases the kids were born without agglutinins, and probably derived it from the mother through the milk, in which it is found accumulated at parturition. From the milk as well as from the kids' serum it disappears in the course of a few days, and then follows a period of a few months in which the blood of the kid is free from agglutinins. After this it reappears, probably from immunization from the flora of the digestive tract. This study was made for coli and typhoid agglutinins, and also for the agglutinins against rabbit and horse-blood corpuscles. In the blood of the kid there was found in some cases more and in others less of the so-called normal antibodies than in the blood of the mothers. Only in one case did the blood of the kid contain more than the colostrum, so that it was not possible to deduce any quantitative rule. It was found that in the colostrum the titer was higher than the serum of the mother. It was shown in one case by nursing experiments that the agglutinins are probably transmitted to the kid through the mother's milk. In another case the result was questionable. The agglutinin maximum of the blood of the kid may occur as early as about eleven hours after birth. By the injections of horse-blood corpuscles into kids it was possible to increase the agglutinating power as well against these corpuscles as against the colon bacillus, and, on the other hand, injection of the colon bacillus increased the agglutinating power against horse blood corpuscles.

Relation of Acquired Food Dislikes of Children to Diseases of Middle Life.—RICE (*Jour. Am. Med. Assn.*, July 10, 1920) says that almost without exception the adults and children possess the red blood and vigor of health are those who eat a variety of foods. They may eat irregularly and consume a great deal of what is called trash, but their appetites for the essential foods remain unimpaired. A healthy individual rarely dislikes eggs, milk, fresh meats or green vegetables. The latter type of food is the most common element in the diet of healthy individuals. A diet without green vegetables and milk is deficient. If

fresh meats are also eliminated serious metabolic disturbances will ensue. It is during the second year of life that children previously healthy on a well-balanced diet become desirous of foods that are seen and which may prove deleterious on account of habit formation even if not in themselves harmful. Discipline is necessary for the future welfare of the child. A large number of sufferers from the diseases of middle life suffer from food dislikes dating back to childhood. Rickets, scurvy, pellagra and beri-beri are due to deficient diets. The author believes that hypertension, chronic Bright's disease, visceral ptosis, gastric and duodenal ulcer and other conditions are the remote graver manifestations of improper diet.

OBSTETRICS

UNDER THE CHARGE OF

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Labor Complicated by Gangrenous Appendicitis.—GRATTAN (*Surg. Gynec. and Obst.*, November, 1919) reports the case of a primipara who had always been healthy and who had been well during the first of her pregnancy. Presentation and position were normal, but when first seen the analysis of the urine was negative. The pregnancy proceeded in a strikingly normal and healthful way. When at term the patient's physician was called by telephone to suggest something to relieve pain in the epigastrium which had started earlier in the evening and increased toward midnight. There was slight nausea, but no distinct pain anywhere. Alkalis and carminatives gave no relief. Gastric lavage and enema were given later and the patient was better throughout the day and evening. The temperature then rose slightly until it reached 101°. There were no labor pains and no distinct abdominal pain. On the next morning the temperature was 100.4°, and for the first time tenderness could be made out in the right iliac and lumbar regions and in lesser degree in the left iliac region. The point of greatest tenderness was high and external to McBurney's point, but this might result from an upward displacement of the intestines by a full-term uterus, and a diagnosis of acute appendicitis was made. The patient began to complain of labor pains, and on examination it was found that the cervix was beginning to dilate. Operation was decided upon and the abdomen was opened by a high and extremely lateral incision. When the peritoneum was opened there was a gush of several ounces of turbid fluid. A tense, fluctuating and sausage-shaped mass was found upward and behind the displaced cecum. This mass was very carefully drawn down into the wound, where it proved to be a completely gangrenous appendix, distended with fluid, but as yet without perforation. The appendix was ligated at its base with catgut and the remainder amputated. Two rubber drains were inserted and the abdomen was closed. The appendix

was firm in shape, dull on the peritoneal surface, the coats thinned by distention and the lumen contained about 2 drams of foul sanguineous pus. The muscular coats of the appendix were in a state of dissolution. There was considerable pressure on the walls of the distended organ. At its proximal end there was a coprolith. There was no omentum adjacent to the appendix. A half-hour after the operation labor began and the patient was given moderate doses of morphin. When the head reached the pelvic floor the patient complained of pain in the wound and chloroform was again given and the head carefully delivered under partial narcosis with forceps. There was no tear requiring suture. The placenta was delivered normally and the uterus contracted well without hemorrhage. The baby's pulse was good and regular, but at first it did not breathe. Oxygen and the lung motor were employed and after thirty-five minutes of intermittent use of this appliance breathing became established and the baby cried loudly. There were no marks of the forceps and no paralysis of the face or extremities. The child weighed eight pounds one ounce. Two and a half hours after delivery the patient had cyanosis and apnea, while the action of the heart continued to be regular. The baby seemed well and breathed and cried. A little later another attack occurred which required one hour and five minutes of artificial respiration, when the child seemed to be doing well. A fourth attack of apnea developed later, heart action failed and the baby died. The infant was catheterized and the urine examined for traces of morphin, thinking that perhaps the three doses administered to the mother might have affected the child. No evidence of the drug was found by toxicologic examination. As the child lived seven and a half hours after delivery, and seemed perfectly normal between the attacks of apnea, with no evidence of paralysis, the forceps could scarcely be considered the cause of its death. The most reasonable explanation of the infant's death was that of toxemia derived from the mother as the result of the appendicitis. A postmortem examination of the child was declined. There was slight nausea and inability to void urine, and fluids were taken in small quantities and the secretion of urine was normal. Later the patient vomited a large amount of mucus and bile-stained fluid. On the following morning there was irregularity of the pulse, although there was no symptom of internal bleeding. The pulse became irregular and rapid. The effort was made to introduce saline fluid and free stimulation was employed. The secretion of urine became more scanty and a large quantity of albumin appeared. Evidently the mother was profoundly toxic and had a toxic myocarditis. The wound did well. The pelvic drainage was removed but symptoms of cardiac failure developed. In spite of stimulation the action of the heart gradually failed, the secretion of urine varied, but slowly increased. On the sixteenth day after the operation the patient had considerable fever, the wound was reopened and a boggy, sanguineous exudate was found on the outer side of the wound. This was broken up and a rubber tube inserted. After this the temperature dropped to normal and the patient made an uninterrupted recovery. The last vaginal examination showed the uterus normal and that there was no residual pelvic exudate, which was unusual under the conditions. The patient finally made a complete recovery. The writer lays considerable stress on the concealed and insidious nature of the appendicitis. In the reviewer's experience this hidden development of infection of the appendix is not uncommon

during pregnancy. In one case a multipara passed through a spontaneous labor, nursed her child, made an apparent recovery and went to her home. Shortly after she was taken with symptoms of infection of the appendix and at operation the infection had attacked not only the appendix but the right Fallopian tube. The appendix was gangrenous and the peritoneum in the right lower abdomen had become infected. With free drainage the patient recovered.

Twenty-four Breech Presentations.—REMY (*Rev. mens. de gynec. obst., et de pediat.*, 1919, 125) reports 17 breech presentations which occurred in his own experience. The delivery was spontaneous in 13 of these. In 4 some obstetric operation was necessary, in 3 for insufficiency of expulsive force and once for the posterorotation of the child's back as well as rotation of the head. In all of the 17 cases a living child was delivered, and most of them breathed well. The writer believes that when uterine contractions are good and the breech and body of the child are born early the obstetrician should lower the arms, which is easily done, and use classical and ordinary methods to secure the expulsion of the head. It is not correct to apply the term dystocia to such cases. These, however, are the most favorable type. In 7 other cases of breech presentation extraction of the child was necessary because of complications. In two the child was dead before anything could be done. In two others (primipara) the child died during delivery. In both of these cases the greater part of the child's body was above the pelvic brim. Of the total number of 11 cases reported in which intervention was absolutely necessary eclampsia was present in 4. In the eclamptic cases a living child was delivered. Because of the complications of breech labor the writer urges that whenever possible the head be substituted for the breech before measures to deliver the patient are undertaken.

Cesarean Section from the Dead and Dying.—LINZENMEIER (*Med. Klin.*, 1920, Nr. 17, p. 439), in four operations upon dead or dying mothers, succeeded in delivering three children alive. In view of the importance of prompt operation, he believes that the operator should not wait until the actual moment of dissolution in the mother. Death is preceded by a period of unconsciousness and this would be the favorable time for operation. In fact, so soon as it is seen that death is approaching, in the interest of the child, the operation should be performed. Acute pulmonary tuberculosis is one of the conditions frequently justifying the operation. Where the patient has rapidly advancing tuberculosis, pregnancy should be interrupted so soon as possible. If, however, the case is not seen until the second half of pregnancy, delay may be practised in the hope of obtaining a living child. In these cases, the operator should not wait until the operation is done as a last resort. With patients where the conditions are all favorable for a rapid and easy vaginal delivery, this may be practised oftentimes including vaginal Cesarean section. If, however, the mother's condition is such that the child is already somewhat injured by the approaching maternal death, abdominal Cesarean section is demanded, because it exposes the child to the least risk and delivers it in the quickest manner possible. If the patient is not comatose, anesthesia must be employed.

GYNECOLOGY

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Periodic Headaches of Ovarian Origin.—In the fall of 1916 a married woman, aged thirty-eight years, came to ABBOTT (*New York Med. Jour.*, 1920, cxii, 724) seeking relief from headaches which she had had for many years, but had become very troublesome only in the last few months. They were coincident with the menses, beginning slightly before and lasting five to seven days. These headaches were entirely absent during pregnancy but always recurred after the termination of gestation. Abbott's attention was at once centered upon the production of the corpus luteum as the possible and probable explanation of this phenomenon. So definite and suggestive was the history that he immediately determined to try the administration of dried corpora lutea. Five grains of a standard product was given three times a day and the patient was instructed to continue this until a perceptible result was obtained and after that to reduce the dose for the next two weeks after each period, but return to the full dose twelve to fourteen days prior to the period. After three months the patient returned, reporting that the headache occurring with the first menses after beginning treatment was not so severe as usual. The second one was but slight, and there was no headache at all with the third period. The patient did not come again for five or six months. At this third visit she reported that she had stopped the medicine entirely after the third month of treatment and that she had no headache for about three months more, when a recurrence took place and the medicine was resumed. For a few times she took the medicine before each period and has had no headaches since the first recurrence. Over two years from the beginning of treatment the patient reported that she had taken no capsules for a year and had had no menstrual headaches. Since treating this patient Abbott has treated about 25 women with headaches of this type and the results have been highly gratifying. With the majority of patients, however, it seems to be necessary to repeat monthly a brief course of corpora lutea prior to each menstrual period. The treatment has never provoked an increased flow or any other untoward symptoms. In order to obtain definite results the cases must be carefully selected, discarding all that do not fall under the definite symptomatology and course outlined. This type of headache always occurs, in the first place, with some definite time relation to the menses. It may be during the period only. It may begin a few hours or even a week

before the period. In some cases it always comes after the close of the menstrual flow. The headaches never occur during pregnancy. This feature has been absolutely uniform in those women who have born children or who have had children since the inception of this type of headache. A third feature of these headaches is that they become worse as the patient approaches the menopause and reach their maximum with the usual height of the nervous symptoms of this period of life. Periodic headaches of ovarian origin cease after the full completion of the ovarian atrophy of the climacteric. The cessation of such headaches will therefore occur after the operative removal of the ovaries for any cause whatsoever and will be very materially hastened by proper dosage of x-ray or radium. When very severe, this type of headache is usually accompanied by nausea and vomiting and for this reason women often speak of them as sick headaches. Care should be observed that this does not lead to confusion with other forms of headache associated with nausea or vomiting, or both.

Exstrophy of the Bladder in the Female.—In looking up the literature on exstrophy of the bladder, BURKE (*Ann. Surg.*, 1921, lxxiii, 100) was unable to find a single instance of operative cure of such a condition in a female subject by the extraperitoneal method and, therefore, presents the detail of a case of this congenital anomaly in a female which he has succeeded in curing. The technic which he followed in this case began with the introduction of catheters in the ureters for about six inches. This served a twofold purpose, (a) as guides, giving definite knowledge of the position and course of the ureters, and (b) as conductors of urine from the ureters, rendering the operation field free of contamination. Beginning at the mucocutaneous border of the bladder, he made a two and a half inch incision through the skin and fat in the median line, down to the rectus fascia and the fascia was split the whole length of this incision. Beginning at the posterior wall of the bladder at the lower end of the incision, with gauze on the index finger, separation of the bladder from the peritoneum was accomplished with little difficulty. The bladder was then completely freed from the abdominal wall and the gauze dissection was continued down to the ureters, which were easily distinguished on account of the catheters previously inserted. After freeing the bladder and isolating the ureters for about one and a half inches, the bladder was split in the middle line down through the trigone. Beginning at this point he incised circularly the bladder about a quarter of an inch away from the ureter meatus, therefore making a button or rosette of bladder with the meatus in the center. In this manner the blood supply as well as the sphincter action of the ureter outlet was preserved. Then two mattress sutures of catgut were inserted into each rosette, leaving the ends long. At this stage of the operation it was necessary for an assistant to dilate the anal sphincter and introduce the index finger into the vagina and the middle finger into the rectum. A long forceps was passed up into the rectum, the middle finger of the assistant acting as a guide, and pushed up to meet the operator's finger from above. Between the operator's finger and the assistant's middle finger were rectal wall and pelvic fascia. A small incision was made over the tip of the forceps and the latter pushed up through

the rectum to grasp the long ends of catgut attached to the bladder rosette containing the ureter opening. The catgut with the ureter was then drawn through the opening made in the rectum and at the completion of the operation the ureters hung suspended for about three-quarters of an inch in the rectum, about one inch above the anal sphincter. In transplanting these lower ends of the ureters it was attempted to prevent any kinking. The remaining part of the bladder was extirpated and iodoform gauze was packed loosely down to the rectum on either side of the vagina, to act, first, to stop the oozing which was considerable, and second, to help prevent the ureters from slipping from the rectum. The abdominal wound was closed in the usual manner down almost to the pubes, just enough opening left to permit the two gauze strips to emerge. The catgut strands hanging in the rectum, attached to the rosettes, were brought outside the anus and kept taut by adhesive plaster in order to prevent slipping back of the ureters from the rectum and a piece of rubber tubing was then placed in the rectum.

Operative Treatment of Bladder Neoplasms.—Although the electrical cauterization of bladder neoplasms has been successfully employed for many years by BEER (*Ann. Surg.*, 1921, lxxiii, 72) since he introduced it to the profession, he has repeatedly urged that this method of treatment should not be employed in malignant growths or in benign growths (a) that are not readily accessible, (b) that surround the sphincter and bleed so that a thorough treatment is impossible, (c) that are so numerous that the bladder is studded with tumors (papillomatosis), and (d) those cases that for one reason or another are intolerant and cannot be regularly cystoscoped. In cases of the above mentioned types, operation must be employed and the technic which has given Beer the best results is as follows: After irrigating the bladder, it is emptied so that when it is opened the wound is not flooded with fluid containing tumor cells, and the patient is placed in the Trendelenburg position and a suprapubic incision is made. The bladder is exposed and freed extraperitoneally and the urachus is doubly clamped and cut. After the bladder is well freed down to the trigone, the perivesical space is packed off with gauze pads and the bladder is incised either through its anterior, posterior or lateral wall, depending upon the position of the growth. Sponging within the bladder should be reduced to a minimum. When the growth is exposed it is immediately cauterized *in situ* with the electric cautery and every suspicious spot is treated similarly, remembering that a too extensive cauterization is preferable to a too superficial one. If the bladder wall is infiltrated, a wide cautery resection of this area is performed. If a ureter is involved in the infiltrated area it is left attached until this area is resected and is then cut away from the resected portion at a distance from the growth and is implanted into a healthy part of the bladder just before the bladder wounds are sutured. The use of clamps with teeth, such as the Kocher, which produce minute perforations in the bladder wall, thus possibly producing implants, should be avoided throughout the operation. In order to further prevent the possibility of bladder implants, the incision which opened the bladder is carefully seared with the cautery and then

the whole wound is filled for about five minutes with alcohol, the bladder being allowed to slip back into its bed so that its cavity as well as the protected gauze is exposed to the effects of the alcohol, which it is hoped will coagulate any potential cell implants that have broken away during the various manipulations. The bladder is then sponged dry and closed, after making provision for suprapubic tube drainage. In closing the bladder, a layer of plain catgut sutures is used to infold the charred edges of the incision and over this a layer of chromic gut is applied to support the first layer. The abdominal incision is closed in layers with rubber dam drainage to the bladder both above and below the tube which enters that organ.

PATHOLOGY AND BACTERIOLOGY

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Complement-fixation in Influenza with B. Influenzæ Antigens.—Complement-fixation tests on serums from thirty-five patients, using several strains of *Bacillus influenzae* as antigens were performed by Cooke (*Jour. Infect. Dis.*, 1920, xxvii, 476). The antigens consisted of moderately opaque saline emulsions from twenty-four-hour blood agar plates, which were heated to 65° C. for one hour and titrated to determine anticomplementary qualities. Inactivated serums in quantities of 0.1, 0.05 and 0.01 c.c. were used for each fixation test. The hemolytic system consisted of two units of complement with 0.5 c.c. of a 1 per cent. suspension of sheep corpuscles, sensitized with two units of hemolysin. Twenty-one of the cases were of uncomplicated influenza and fourteen had bronchopneumonia, one of which was fatal. The blood for testing was obtained after the temperature was normal, usually in the second week after the onset of the first symptoms. In all, 162 tests were made on 24 sera of older children and adults, using 16 strains of *Bacillus influenzae* and over 60 per cent. of the reactions were positive. Of 59 tests on eleven children with 8 strains of *Bacillus influenzae*, only 17 were positive, 6 of these being weak reactions. The controls included 13 cases, and of the 120 tests done 16 per cent. were positive. One of the positive reactions was given by the serum of an apparently healthy carrier. No specific antigenic relationship could be detected between the 16 strains of *Bacillus influenzae* with the serums tested. The author concluded that the complement-fixation test could not furnish sufficient evidence to justify the conclusion that *Bacillus influenzae* is the sole etiologic agent in influenza although the results indicated that the influenza bacillus is pathogenic and infects many, if not all, patients with influenza.

Experimental Study of the Mononuclear Phagocytes of the Lung.—The importance of endothelial reactions in the bodily defense has long been urged by Mallory. Their activities in the lung were studied by Haythorn, largely from the standpoint of the disposition of inspired dust and carbon particles in anthracosis. From experimental work as well as the study of human tissues, he concluded that the dust cell was of endothelial derivation, though he could not be specific as to its point of origin. Six years after this work, Sewell reverted to the earlier theory that the dust phagocytes were derived from the respiratory epithelium. Recently, PERMAR (*Jour. Med. Res.*, 1920, xlii, 9), using intratracheal injections of particulate matter (carmine powder in suspension) combined with simultaneous and subsequent *intra vitam* staining (isamine blue) in experimental animals, has been able to demonstrate that the endothelium of the vascular bed of the lung gives rise by proliferation to wandering endothelial phagocytes, the endothelium of the blood capillaries being especially active in this regard. These wandering endothelial cells migrate directly to the air sacs, to serve immediately as active phagocytes for the foreign particulate substances lying there. The endothelial phagocytes were shown to be identical with "dust cells" and could be followed from this origin in the vascular endothelium, and subsequently wandering through the interstitial tissues into the air-sacs, where they phagocytized carmine granules. Further, these cells were found in lymphatics, migrating toward the hilus, and also in the lymph nodes at the hilus. The rate of endothelial proliferation was shown to be directly dependent on character and the intensity of the irritant employed in the intratracheal injection. Phagocytosis was found to begin within one hour, and to be well established after six hours; while at the expiration of twenty-four hours practically all pigment had been taken up by the numerous free endothelial phagocytes present. The rate of migration was fairly rapid, carmine bearing mononuclears being found in the peribronchial lymph nodes within twenty-four hours. This does not continue at this rate, however. The respiratory epithelium was never found to contain pigment granules, nor did it ever show evidence of contributing to the production of mononuclear phagocytes. The mononuclear leukocytes of the circulating blood could also be ruled out, since none of the blood cells took vital stain under the condition of administration.

Intestinal Obstruction: A Study of the Influence of the Bacterial Flora on the Toxemia of Acute Obstruction.—It has been demonstrated that the material which collects in the intestine above the point of obstruction is toxic and that the absorption of this material is responsible for the toxemia of acute obstruction. That the toxic materials in intestinal contents both under normal conditions and in cases of acute obstruction may arise independently of food and in the absence of gastric juice, pancreatic juice and bile has been shown, as has the fact that the secretions of the normal intestinal mucosa are not toxic when absorbed from the peritoneal cavity. It seems probable that the principal toxic factor in the contents of the obstructed intestine belongs to the group of poisonous substances which are produced by the action of bacteria on proteins or their split products. CANNON, DRAGSTEDT and DRAGSTEDT (*Jour. Infect. Dis.*, 1920, xxvii, 139) studied the rela-

tionship of the intestinal flora to the toxemia resulting from complete obstruction induced by occluding the distal end of the cecum in white rats. Before and after operation, the intestinal flora was controlled by diet. It was found that, at death, proteolytic floras supplanted aciduric ones, in spite of the diets fed. The average period of survival was longer in the rats previously fed with bread, milk and lactose than those fed on meat. The authors conclude that it is not possible to prevent the onset of toxemia in acute intestinal obstruction by feeding diets which in normal animals bring about an aciduric intestinal flora, but they believe the onset of toxemia may be delayed in proportion to the degree that the aciduric flora may be maintained, presumably developing simultaneously with the appearance of a proteolytic flora.

Bacillus Perfringens: Toxin and Antitoxin Production.—Although the urgency for an antiserum against gas gangrene has largely subsided with the cessation of war, a sufficient number of cases are encountered in civil practice to warrant further work for practical and scientific purposes. CAULFIELD (*Jour. Infect. Dis.*, 1920, xxvii, 151) has recorded certain observations made in the production and standardization of an antiserum to *Bacillus perfringens* and a combined antiserum to *Bacillus perfringens* and *Bacillus tetani*. Fresh muscle glucose broth, as advised by Bull and Pritchett, was adopted in the preparation of toxin. Utmost care was necessary to maintain virulence and every attempt to raise the virulence by direct animal or bird (pigeon) passage failed, while virulence could be increased by cultural methods. By injection of pigeons with short incubation cultures, it was found that even six to eight hours' incubation produced a culture of high virulence. To avoid loss of toxicity during filtration the time involved was shortened by passing the oil-covered cultures through paper mash and then through a medium Berkefeld candle into colored glass bottles containing a few c.c. of sterile paraffine oil. The antiserum was standardized by neutralization as shown by absence of reaction at the site of inoculation into the pigeon breast muscles. Two M.L.D's of toxin were used as the test dose and the smallest amount of serum which would allow the bird to survive thirty-six hours was determined. The serum toxin mixture was incubated for one hour and the smallest amount of serum required to save the life of the bird estimated as one antitoxin unit. The most effective antiserum was the monovalent which protected against two M.L.D's of the toxin in a dilution of 1 : 200. No practical difference was noted between deaths due to whole cultures and toxins. The interval between the time of inoculation and death in the pigeon was rapidly shortened by comparatively slight increase in the dose. The sera of two horses immunized against *Bacillus perfringens* developed a titer of from 1 : 600 to 1 : 800. By concentration methods it was found that the horses treated with *Bacillus perfringens* developed as many as 40,000 antitoxin units per c.c., while those receiving both *Bacillus perfringens* and *Bacillus tetani* developed up to 15,000 for the former and up to 700 for the latter.

HYGIENE AND PUBLIC HEALTH

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Production in Monkeys of an Acute Respiratory Disease Resembling Influenza by Inoculation with *Bacillus Influenzæ*.—BLAKE and CECIL (*Jour. Exper. Med.*, December, 1920, No. 6, xxxii, 692) state that *Bacillus influenzae* can initiate in normal monkeys an acute infection of the upper respiratory tract which may be complicated by acute sinusitis, tracheobronchitis, hemorrhagic edema of the lungs, bronchiolitis, and bronchopneumonia. This disease appears to be essentially identical with influenza with respect to its clinical course, symptoms, and complications. The etiologic relation of *Bacillus influenzae* to acute sinusitis, tracheobronchitis, bronchiolitis, and bronchopneumonia is established. Although it seems reasonable to infer from the results of the experiments that *Bacillus influenzae* is the specific cause of influenza, a definite conclusion is not permissible, since it is impossible to determine whether the respiratory disease produced in monkeys with *Bacillus influenzae* is identical with influenza or merely similar to it. The experiments are advanced, therefore, as evidence in favor of the etiologic relation of *Bacillus influenzae* to influenza.

Studies on Experimental Pneumonia. (X) Pathology of Experimental Influenza and of *Bacillus Influenzæ* Pneumonia in Monkeys.—CECIL and BLAKE (*Jour. Exper. Med.*, December 1, 1920, No. 6, xxxii, 719) found that virulent influenza bacilli, when injected into the nose and throat of monkeys (*Cebus capucinus* and *Macacus syrichtus*), excite an acute inflammation of the upper respiratory tract, characterized by swelling and hyperemia of the mucous membrane, infiltration of the mucosa and submucosa with leukocytes, desquamation of epithelial cells, and the production of a mucopurulent exudate. The accessory sinuses are often implicated in the infection. Experimental *Bacillus influenzae* infections of the upper respiratory tract are frequently accompanied or followed by bronchiolitis, peribronchial infiltration, and bronchopneumonia with hemorrhage and edema in the early stage, emphysema and bronchiectasis in the later stages. In general, the process closely resembles uncomplicated *Bacillus influenzae* pneumonia in man. The injection of virulent influenza bacilli directly into the trachea of monkeys induces in them an experimental bronchiolitis and hemorrhagic bronchopneumonia, similar in all respects to spontaneous *Bacillus influenzae* pneumonia. In experimental *Bacillus influenzae* infections of either the upper or lower respiratory tract the influenza

bacillus can usually be recovered during the acute stage by culture, either pure or in association with other bacteria. In experimental *Bacillus influenzae* infections in monkeys characteristic changes occur in the thymus gland—hyperplasia of the follicles, distention of the lymphatic channels, and infiltration of the parenchyma with leukocytes. This enlargement appears to be merely part of a general hyperplasia of the lymphoid structures in the cervical and thoracic regions.

Chilling of the Body Surface in Relation to Auto-infections of the Upper Respiratory Mucous Membranes.—GRANT, MUDD and GOLDMAN (*Jour. Exper. Med.*, 1920, xxxii, 87-112) report improvements in a method previously described (*Jour. Med. Research*, 1919, xl, 53-101) for detecting alterations in the blood supply of the throat by following with thermophiles, applied to the mucous membrane and skin, local temperature changes. The palatine tonsils, like the palate, pharynx and skin, react to chilling of the body surface with reflex vasoconstriction and ischemia. On rewarming the subject the tonsils tend quickly to recover their blood supply, in some instances actually becoming hyperemic; the skin returns to about its control condition; the palate and pharynx remain somewhat ischemic. The hypothesis is advanced that one factor in the beneficial hardening effect of cold bathing and outdoor living, with its incident heightened resistance to respiratory infection, may be the training of the vasomotor system in the direction of development in the pharynx of a reaction of hyperemia following chilling, similar to that observed in certain instances in the tonsils of the present subjects. The flora of the pharynx and tonsils, studied with daily swabs, showed in several instances, after experimentation, changes apparently due to proliferation of one of the microorganisms already present. In one case *Streptococcus hemolyticus*, in one *Micrococcus catarrhalis*, and in a third *Bacillus influenzae* was the organism showing a relative increase in numbers. The first two instances were associated with sore-throat, the third with slight constitutional symptoms. Because of trauma and other factors it is by no means clear that these bacterial changes had anything to do with the chilling. However, it seems at least likely that the mucous membrane ischemia resulting from prolonged or excessive chilling might so lower local resistance as to permit of auto-infection. The fact is emphasized that *excessive* exposure only is warned against. Good ventilation and circulating air in buildings, cold weather and out-of-door living are needed for vigorous health; many people are unquestionably benefited by cold bathing. It is also emphasized that colds dependent primarily upon contagion from outside sources are probably of more frequent and widespread occurrence than auto-infections.

Some Possibilities in the Statistical Analysis of Case Reports of Venereal Diseases.—PIERCE and SYDENSTRICKER (*Public Health Reports*, August 27, 1920, No. 35, xxxv, 2046), in a preliminary statistical study, present data indicating that (1) the highest incidence of venereal diseases occurs at nineteen years for females and about two years later for males; (2) the highest incidence is earlier among negroes than among whites; (3) gonococcus infections in both males and females occur earlier in life than does syphilis.

Children's Teeth, a Community Responsibility.—CLARK and BUTLER (*Public Health Reports*, November 19, 1920, No. 47, xxxv, 2763) in their introduction dwell on the prevalence of decayed teeth and the necessity for prophylactic measures. In addition to bacteria, the following are given as actual and potential *causes of dental decay*: (1) Low resistance of the teeth to decay because of developmental defect (antenatal and postnatal). (2) Faulty diet, both of the mother during pregnancy and of the child. (3) Neglect of dental attention through ignorance of parents. (4) The cost of dental attention, a serious consideration with families of low economic status. (5) Failure of the child to call attention to the condition of the teeth, either because it is too young or because of fear. (6) Lack of dental facilities, so common in rural sections. The effects of dental decay are considered with reference to (1) growth; (2) resistance to communicable diseases; (3) preservation of facial symmetry, and (4) degenerative diseases. Mouth hygiene is discussed and the details of community prophylaxis are considered in considerable detail. The relation of dental clinics to parents and guardians, school authorities and taxpayers, is set forth. The choice of a toothbrush and the use of this article are considered in detail. Lime water is recommended as an effective mouth wash.

One or Several Species of Malaria Parasites.—MAYNE (*Public Health Reports*, November 26, 1920, No. 48, xxxv, 2846) refers first to the practical importance of classification of types of malarial fevers from the standpoint of treatment. The literature bearing on the numbers of species of malarial parasites is reviewed and the writer's own experience is presented. It is shown that in experimental transmissions the infection conveyed runs true to type, and the author expresses the opinion that plurality of species is the normal status.

Ambulatory Treatment of Drug Addiction.—The U. S. Public Health Service (*Public Health Reports*, December 3, 1920, No. 49, xxxv, 2914) reviews the administrative factors of the ambulatory treatment of drug addicts. It is pointed out that legal opinion is expressed that this form of treatment is presumptively a violation of the Harrison Narcotic Drug Law. The order of the Commissioner of Health of Pennsylvania in prohibiting ambulatory treatment is given, as well as comments on the opening of a "clinic" in New York City, and the opinion of a Committee of the Institute of Criminal Law and Criminology.

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ORIGINAL ARTICLES.

PELLAGRA.

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Definition. Pellagra is a specific disease of man characterized by clinical manifestations on the part of the digestive tract, the nervous system and the skin. The digestive tract presents various grades of inflammation. The nervous system manifests varying grades of toxic reaction, ranging from peripheral neuritis to toxic psychosis, or the lethal central neuritis. The cutaneous eruption is the most characteristic feature of pellagra. It is a symmetrical erythema involving especially the backs of the hands, and it has the same importance in the diagnosis of pellagra as has the eruption of measles or of smallpox in the diagnosis of those diseases.

Etiology. Specific Causation. The specific cause of pellagra is unknown. There are numerous theories championed by one or more students of the disease, some of them definite, others quite nebulous. Roussel, in 1866, presented the zeistic theory in such definite form and supported it by such clearly marshalled facts that from his day until 1905 this conception of pellagra remained almost unchallenged. According to Roussel, pellagra is due to two factors or groups of factors, of which one is external and the other resides within the human body itself. The extrinsic factor is altered maize, which is the special and specific cause of pellagra, giving to the disease its character as a pathologic entity and without which the other etiologic factors are powerless to produce this malady. However, in order to be effective, the altered maize is not alone sufficient,

since observation proves that its abundant use often fails to produce pellagra; it requires in addition to encounter within the body of the victim certain conditions of vitality, just as parasites need to encounter appropriate susceptible hosts and as seeds require suitable soil for their development. All causes of enfeeblement, particularly the phases of sexual activity in the female and above all the factor of heredity, create this necessary vital condition of susceptibility. Such, says Roussel, is the dual basis indispensable as a solid foundation for the etiologic theory of pellagra. Much in this view of Roussel still merits admiration and respectful consideration. In 1905 Sambon launched a most effective attack against the maize theory, and it is now almost universally recognized that pellagra occurs in those who do not eat maize, the possibility of which was absolutely denied by Roussel in his time. Sambon, unfortunately, coupled with his refutation of the maize theory the thesis that pellagra is an insect-borne infectious disease, transmitted by a fly of the genus *Simulium*, a theory which has not been able to survive in the subsequent study of pellagra.

In 1911 the Illinois State Pellagra Commission, after extensive studies of outbreaks of pellagra in institutions for the insane over a period of two years, drew the following conclusions:

1. According to the weight of evidence pellagra is a disease due to infection with a living microörganism of unknown nature.
2. A possible location for this infection is in the intestinal tract.
3. Deficient animal protein in the diet may constitute a predisposing factor in the contraction of the disease.

This commission recommended an increase in the animal protein of the dietaries of the state hospitals and advised compulsory notification of all cases of pellagra. The Robert M. Thompson Pellagra Commission, after extensive study of pellagra in the general civilian population of the Southern United States and in the West Indies, in the course of which particular attention was given to the maize theory and to Sambon's theory of insect transmission, has come to conclusions supporting the Illinois Commission. Jobling and Peterson and their co-workers, as a result of their extensive epidemiologic studies in Nashville and vicinity, also incline to the same view.

Sandwith, in 1912, raised the question whether pellagra might not be a disease essentially due to a deficiency of nutrition, and he pointed out certain analogies between pellagra and beriberi. This theory has been enthusiastically supported by Funk and by Goldberger and their followers. Particularly striking evidence in favor of this theory is found in the elimination of pellagra from eleemosynary institutions by radical improvement of the dietary. That such results admit of another interpretation is evident, as was pointed out by the Illinois Commission in 1911. In November, 1916, Goldberger and Wheeler announced the experimental production,

by means of a deficient unbalanced diet, of a "typical" eruption justifying a diagnosis of pellagra in six of eleven human subjects experimented upon. Because of the official position of these authors this definite and positive announcement, although a mere preliminary communication unaccompanied by detailed facts and illustrations, received wide recognition as a real and valid discovery. The full report, which has now appeared after a delay of more than three years, reveals that what the authors at first designated as a "typical" eruption was actually a dermatitis on the scrotum and apparently on the opposed surfaces of the thighs also in some of the individuals. Apparently the authors no longer wish to maintain that this is a "typical" eruption justifying the diagnosis of pellagra, for in the full report they avoid this expression, and furthermore even express a doubt as to whether their experimental diet was of the specific quality necessary to cause the usual eruption of pellagra. Sullivan made a biologic study of the diet employed by Goldberger and Wheeler, and with it he induced polyneuritis and paralysis in experimental animals, which condition he was able to prevent and even to relieve after its development by the administration of extracts of rice polishings. McCollum, who with his collaborators has carried out an extensive series of studies upon diets of this type, has finally expressed his conviction that pellagra is an infectious disease.

Perhaps the most serious difficulty for the deficiency theory has arisen during the period of the recent war. Dietary deficiency became the rule in central Europe and the resulting increase in debility and in death-rate have been conspicuously reported. Among the diseases increased in this part of Europe during the period of deficient diet, pellagra is conspicuously absent. Actually there was observed an extensive outbreak of pellagra in a British camp for Turkish prisoners of war located in Egypt. Many of these prisoners had evidently been pellagrins before capture, but the disease also spread to new victims in the prison camp. This outbreak of pellagra was investigated by a British Committee of Inquiry, and they ascribed it to the relatively deficient diet of the Turkish prisoners, contrasting, in their report, their condition with that of the German prisoners in an adjacent camp, men who had subsisted on a most excellent diet before capture and who were receiving as prisoners a diet above reproach. Enright has since reported an extensive outbreak of pellagra in this very camp of German prisoners, the outbreak having begun at almost the exact time that the above-mentioned Committee of Inquiry had completed its investigations, namely, December, 1918, and January, 1919. Enright concludes, "Although I have been unable to advance any satisfactory cause for this mysterious outbreak of pellagra, I do submit that I have established a clear case against a 'food deficiency' as being the only factor involved."

In my own opinion the etiology of pellagra depends upon two factors analogous to those recognized by Roussel: (1) The specific causative factor which is a living organism, an infectious agent derived directly or indirectly from a previous case of the disease, and (2) a factor or group of factors, quite non-specific, which serve to reduce the resistance of the victim. In this latter group are recognized malnutrition, either from inadequate food or inability to utilize food in an adequate manner, cachexia of disease, overwork, depressing influence of hot weather, strain of reproduction in women, involution of old age, alcoholism and many other such influences. The specific causative factor, which I believe to be a living organism, remains unrecognized. Most probably it resides in the gastro-intestinal tract, and the absorption of its products from the digestive tract gives rise to the distant manifestations of pellagra. In regard to the factors influencing the possible transmission of the hypothetical parasite, as well as those which may influence the resistance of the human individual, a great many facts have become established by epidemiologic studies in pellagrous districts, some of which are next to be considered.

Geographical Location. Isolated cases of pellagra are occasionally observed in various parts of the world. In view of the chronic and recurrent nature of the disease and the extent of modern travel, such observations are to be expected. In general, however, the relationship between place and origin of pellagra is one of the most striking features of the disease. Pellagra is contracted where there is a preëxisting case of the disease. Its apparent sporadic origin is so rare as to warrant a grave doubt as to the accuracy of diagnosis or the adequate search for preëxisting cases in such instances. Of the thousands of children suffering from malnutrition and lack of food seen every year in the hospitals and clinics of large cities outside pellagra districts, none suffer from pellagra. In pellagrous districts, on the other hand, a very considerable proportion of persons, and especially the children, suffering from lack of food, diseases associated with malnutrition or other depressing conditions, contract pellagra.

Pellagra is prevalent in certain parts of Turkey, Egypt, Roumania, Austrian Tyrol, Northern Italy, West Indies, Yucatan and the Southern United States. Outbreaks have been reported in South Africa and in the Malay States. Outbreaks of considerable importance and sometimes persisting for several years have been observed in the Northern United States, especially in institutions for the insane. In the geographic areas where the disease prevails its distribution is extremely uneven.

Even in the small communities where pellagra is most prevalent the degree of proximity to a pellagrin shows a significant relationship to the danger of contracting the disease. Thus the Thompson-McFadden Commission, in 1913, observed a pellagra incidence of

6.59 per cent. among persons living in the same house with a pellagrins, 1.72 per cent. among persons living next door to such a house and 0.52 per cent. for those living farther away than next door but in the same village communities. This house relationship of pellagra has been confirmed by the subsequent third report of the same commission and also by the independent work of Jobling and Peterson.

Race, Age and Sex. The relationship of race to pellagra is apparently in part directly dependent upon racial variation in resistance to the disease, but in part indirect because one race may be relatively segregated, may be less prosperous or may live upon poorer food. In Spartanburg County, South Carolina, up to October 15, 1914, the negro population of 28,507 had shown 153 recorded pellagrins, an incidence rate of 54 per 10,000, whereas the white population of 62,119 had shown 1027 recorded pellagrins, an incidence rate of 165 per 10,000. This lower incidence in negroes occurred in conjunction with greater poverty of this race and a diet poorer in quality, quantity and variety. The negro population was for the most part relatively segregated from the white race, and thus from the white pellagrins and the incidence of pellagra in the negroes was lowest in those sex and age groups most completely segregated in this way. Although much less frequently attacked by pellagra, the negroes when attacked suffered most severely. Of the 153 cases in negroes, 64, or 41.8 per cent., terminated in death in the first year of the disease, whereas in the white race the analogous death-rate was only 12 per cent. The higher death-rate may express a lower racial resistance to pellagra, but, in part at least, it would seem to be correlated with the greater poverty and the poorer diet of the negro race. No less than 113 of the 153 negro cases occurred in females over sixteen years of age, namely, that portion of the negro race which is least effectively segregated from the white race.

The age at onset of pellagra in each race and sex in the Spartanburg statistics is indicated in Figs. 1, 2 and 3. It is evident that white women and children, older white men and negro women furnished the bulk of the cases. Pellagra is rare in the first year of life, fairly prevalent in white children under ten years of age, distinctly less prevalent at about the age of puberty, again increasing to maximum frequency in women in the age period sixteen to forty-five years, but remaining infrequent in men until after the thirty-second year. The greater prevalence in women during the active period of life is a most remarkable feature. The occurrence of pellagra in children of any district is a feature which stamps the district as an endemic focus of the disease.

The death-rate from pellagra in the initial attack is lowest in children and relatively quite low in women in the age period sixteen to forty-five years, indicating that the factors which bring about an attack of the disease are not identical with the factors which determine a fatal outcome of the attack. In children, pellagra would

appear to present no more serious danger than measles, while in both men and women more than fifty years of age the death-rate is well above 20 per cent. in the first year.

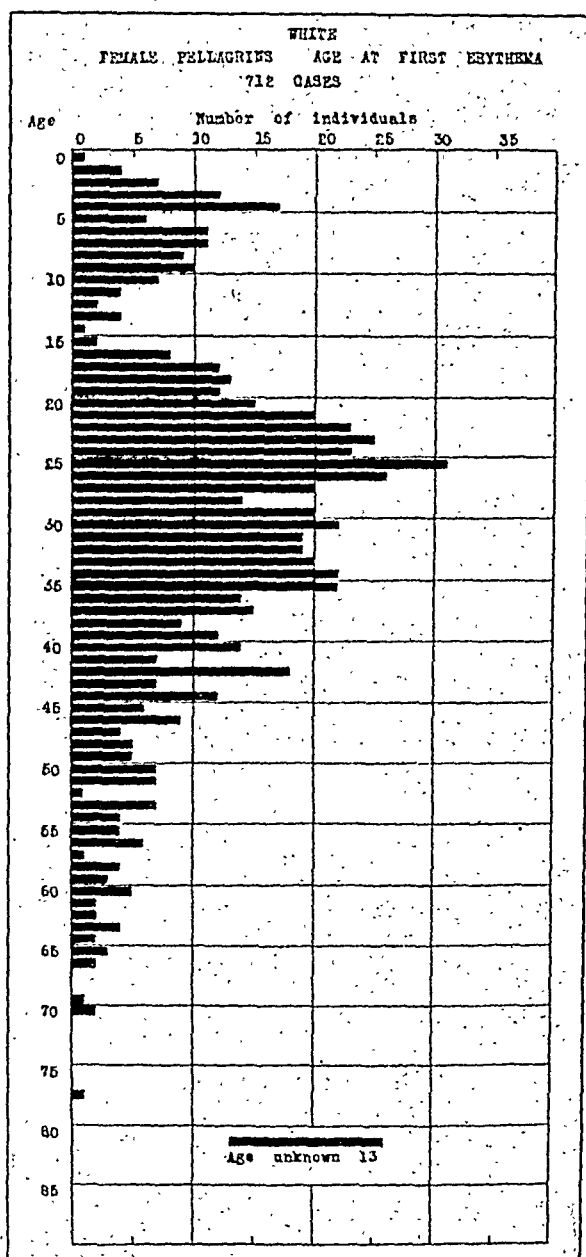


FIG. 1.—The age at onset of initial erythema in the 712 white female pellagrics of the Spartanburg County series. The age distribution is shown for 699 cases. In 13 cases the age was not ascertained. The small number of initial attacks from the eleventh to the sixteenth year is remarkable. (After Siler, Garrison and MacNeal.)

Relation to Food. The older theories assumed that pellagra is due to the toxic action of maize in the diet. It is undoubtedly true

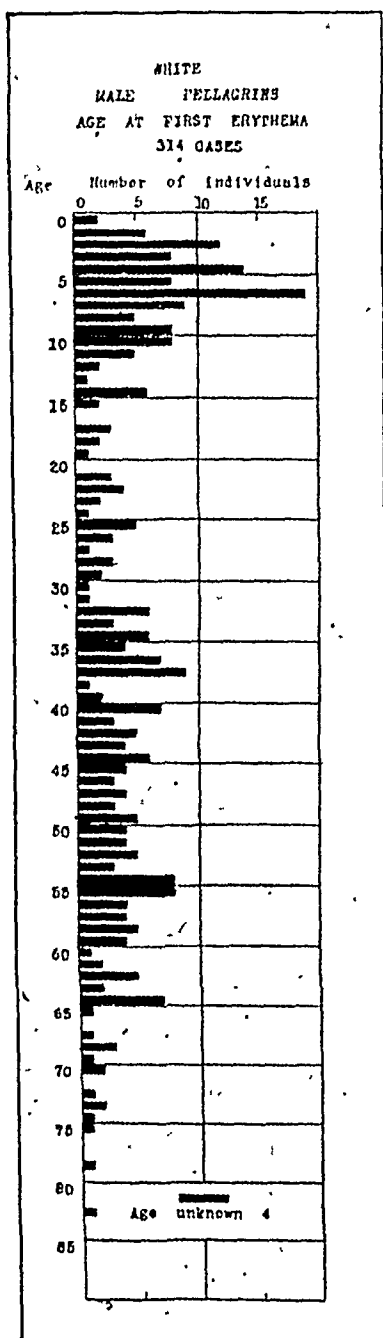


FIG. 2.—The age at onset of initial erythema in the 314 white male pellagrins of the Spartanburg County series. The age distribution is shown for 310 cases. In 4 cases the age was not ascertained. (After Siler, Garrison and MacNeal.)

that the vast majority of pellagrins have eaten maize or maize products, but feeding experiments with and without maize in

endemic foci of pellagra have failed to reveal any greater incidence of pellagra in those taking the large quantities of maize. Further-

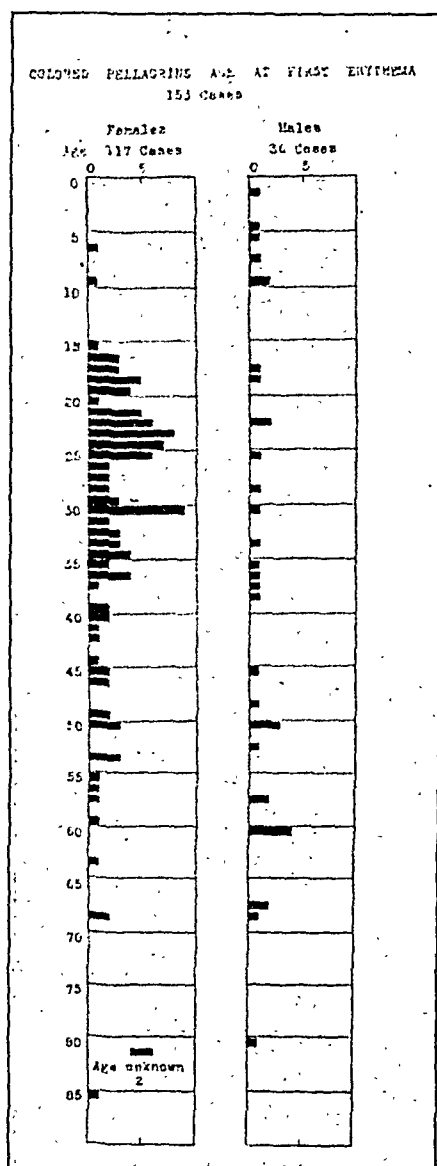


FIG. 3.—The age at onset of initial erythema in the 153 negro pellagrins of the Spartanburg County series. (After Siler, Garrison and MacNeal.)

more, the prophylactic exclusion of maize from the diet of pellagrous families has proved to be a failure, for under these circumstances there have been observed not only recurrences of the disease in those

already affected but also the outbreak of new cases in other members of the family. Perhaps even more convincing has been the report of Stannus of pellagra in prisoners who had had no maize for years, and of Viswalingham, who observed an outbreak of pellagra in Chinese coolies whose diet contained rice as the principal element and contained no maize. The Thompson-McFadden Commission, in 1913, failed to find a positive correlation between the frequency of use of any single food and the frequency of occurrence of pellagra. At present it would seem that no one seriously maintains that pellagra is caused by any single food. There remains, however, the possibility that the excessive use of certain foods, maize for example, may predispose to the development of the disease or render the attack more severe.

A second possibility is that the absence or insufficiency of certain dietary elements, rather than the excess of a certain element, may bear an etiologic relation to pellagra. The pellagra-preventing value of animal foods, especially milk, emphasized by the Illinois Commission and clearly demonstrated by the Thompson-McFadden Commission, is now generally recognized. Recently even Goldberger and his colleagues of the Public Health Service (1920) seem to have abandoned the advocacy of beans in favor of milk, milk products and fresh meat as preventive diet for pellagra. In my own opinion the relative pellagra-preventing value of these foods is similar to their value in preventing tuberculosis. They bring about improved nutrition and increased resistance to the specific cause of the disease. That the mere lack of animal foods is not the specific cause of pellagra is shown by the host of strict vegetarians who escape the disease. Furthermore, a relatively brief study in a pellagrous district suffices to disclose pellagrins who have taken milk daily all their lives, particularly young children, and occasionally one finds adult pellagrins who have eaten meat every day for years.

There remains a third possibility, namely, that general insufficiency of food may play an etiologic role. The theory that such insufficiency may be the specific cause of pellagra has already been discussed and rejected. There can be no question, however, that adequate nutrition is a most important factor of insurance against pellagra and in bringing about recovery from it, and that inadequate nutrition is a most important factor in predisposing to the development of pellagra in those who are exposed to the essential cause by residence in pellagrous districts.

Sanitary Disposal of Sewage. The association of poor sanitation with pellagra prevalence has been mentioned by many authors. The Thompson-McFadden Commission (1913) emphasized the fact that pellagra originates where insanitary surface privies are used and much less frequently where sanitary water-carriage systems of sewage disposal are properly employed. Such a relationship might

be explained by assuming that better sanitation increases the resistance to disease in general or that it operates by preventing the transfer of the specific cause of pellagra from the digestive tract of one person to another. An experimental test of this latter hypothesis was undertaken at Spartan Mills, S. C., in 1913, and the observations were carried through to August, 1916. Following, and apparently as a result of the installation of the sewer system, new cases of pellagra practically ceased to originate in the population of this village, whereas the old cases continued to suffer recurrences of pellagra about as would have been expected had no change in sanitation been undertaken. This relationship of sanitation to pellagra has been confirmed by the studies of Jobling and Peterson. The experiment at Spartan Mills has recently been attacked by Goldberger and Wheeler (1920), who state that they recorded 37 first-attack cases in Spartan Mills Village in 1917 (a year in which the original investigators were unable to continue their observations). The data to support this statement are referred to as "unpublished."

Experimental Inoculation.—Up to the present time the attempts to produce pellagra by experimental inoculation have failed in every instance to yield a conclusive positive result.

CLINICAL MANIFESTATIONS AND COURSE.

Introduction. Strambio described the signs and symptoms of pellagra in three stages of the disease. Roussel, although he did not follow Strambio's classification, nevertheless recognized three stages, not well separated from each other, which he designated as (1) commencing pellagra, (2) confirmed pellagra and (3) pellagrous cachexia. It seems to me preferable to regard pellagra as essentially a chronic disease presenting periods of activity and periods of quiescence, both of somewhat variable duration. According to this conception pellagra may best be studied clinically in two phases: (1) The period of active attack and (2) the interval between attacks. In the former period one may recognize a prodromal stage, an erythematous stage, a stage of hyperkeratosis and desquamation and a stage of sequelæ and convalescence. In the interval between attacks a great many various manifestations may be presented, some of them doubtless due to pellagra, but many of them depending upon quite other factors. The decision concerning the relative importance of pellagra and of other complicating disorders during this interval presents very great and often insuperable difficulties.

The Initial Active Attack. Prodromal Period. Pellagra sometimes begins suddenly with a cutaneous erythema as the first evidence of illness. More frequently there is a prodromal period varying from a few days to several months in length, during which

the patient is aware of diminished physical vigor; lessened appetite or distaste for particular foods or for all food, a burning sensation in the mouth and epigastrium, on the palms of the hands and the soles of the feet; attacks of vertigo, sometimes actual falling to the ground; depression of mind and spirit, evidenced by sadness and tardiness in thought, speech and action; pains in various parts of the body, especially headache, backache, pain and tenderness along the peripheral nerve trunks. Objectively there is often loss of weight, sometimes considerable; in women scanty or suppressed menstruation. Not infrequently there is diarrhea, more or less severe, but in many cases a persistent constipation or no evident disturbance of defecation. Reddening of the mucous membrane of the mouth and pharynx often accompany the burning sensation. Salivation is sometimes present. In patients carefully observed during this period one may occasionally detect an evanescent prelude erythema, first described by Merk. This eruption consists of numerous discrete red macules gradually fading into the surrounding skin, not raised above the skin surface and completely obliterated by slight pressure. It appears on the backs of the hands and forearms and may persist from a few hours to two or three days. This prelude erythema is probably not rare, but it is rarely observed. Pellagrin 597 of the Spartanburg series presented such a transient erythema on May 3, 1913, which disappeared in forty-eight hours and was followed by a frank and definite pellagrous eruption in June of the same year.

None of these prodromal symptoms or signs is sufficiently characteristic to warrant a certain diagnosis of pellagra, but the presence of many of them combined in the same individual in a pellagrous district is strong presumptive evidence of an impending attack of this disease, especially when a careful examination of the patient fails to reveal any other explanation of the observed manifestations. Even after the characteristic, diagnostic eruption subsequently appears, one is still left in doubt as to the relative importance of pellagra and of other complicating or predisposing factors in the causation of these interesting prodromal signs and symptoms.

The Stage of Active Eruption. The typical pellagrous eruption appears suddenly, ordinarily overnight, as a diffuse erythema or as separate red macules quickly becoming confluent, on the knuckles, dorsal surfaces of the phalanges and hands, gradually extending onto the wrists and forearms. At the same time or subsequently an eruption of similar character may appear elsewhere, especially on the forearms, the dorsal surfaces of the feet, the face, back of the neck, sternal region, upper arms, legs, perineum, scrotum, axilla and very rarely on the palms of the hands and the soles of the feet. Merk, who has presented the best clinical study of the cutaneous manifestations of pellagra, considers these eruptions in unusual locations, which he designated as "*atypische*," to be of no significance

for the diagnosis in the absence of the typical eruption on the backs of the hands.

The typical erythema is due to hyperemia, which causes not only redness but also swelling of the area above the level of the adjacent skin. The small flat areas, "fields," of the skin become more prominent while the furrows between the fields become deeper. As a rule the erythema becomes confluent within a few hours and then slowly extends, with a rather sharply demarcated margin. During this stage of progressive erythema the skin is very sensitive to external irritants, such as sunlight or even contact with the air. The sensation is that of burning. Itching may be complained of, but there is never any sign of scratching.

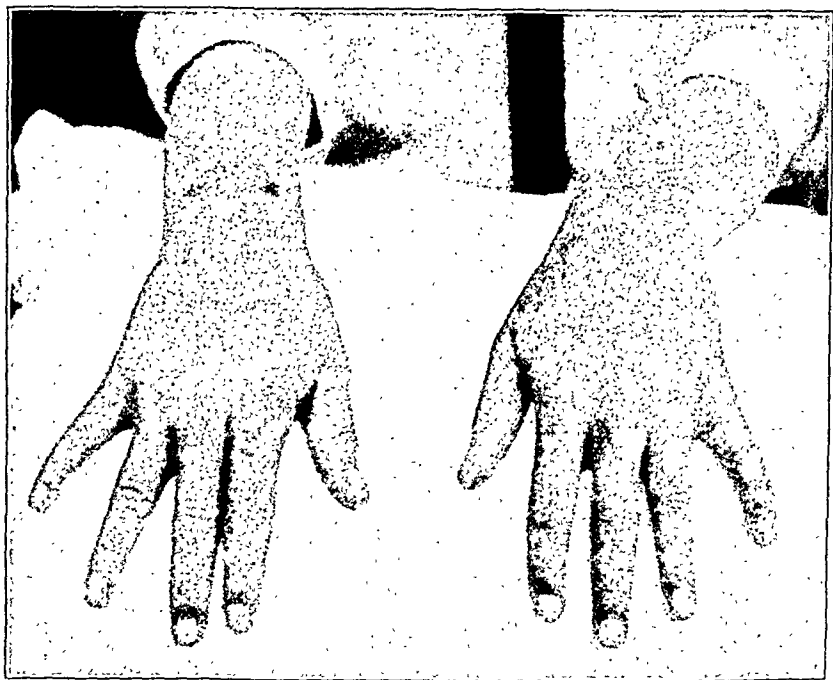


FIG. 4.—Typical pellagrous eruption in an adult male, in the stage of progressive erythema. (Photograph of the Thompson Pellagra Commission.)

Within the first few days the erythematous area begins to show increased desquamation in the form of fine scales, and in from one to two weeks the thickening of the horny layer of the skin with continuing desquamation obscures the underlying erythema. This hyperkeratosis becomes the most characteristic feature of the eruption during the greater part of its course. Thickening of the epidermis and desquamation continue for a variable period, two weeks to several months, usually about four weeks. In brunettes increased pigmentation also appears and is sometimes a marked feature of the erythematous area. Eventually the eruption tends

to disappear, the desquamation exposing a thin, parchment-like, smooth epidermis, more translucent than normal, with a pink, somewhat hyperemic dermis beneath. This restitution begins at the older parts of the lesion and gradually extends, so that the margins of the eruption persist longest. Indeed, in some patients one may observe at the same moment a narrow marginal zone of red, slowly advancing onto healthy skin, followed by a somewhat broader zone of deeply pigmented hyperkeratosis, this in turn succeeded by a still more extensive rough, scaly zone of desquamation, leading over into an area of atrophic smooth skin, where the eruption has completed its course. Occasionally one sees a new outbreak of erythema on the backs of the hands while there still remains the pigmented desquamating margin of a previous eruption on the upper forearms.

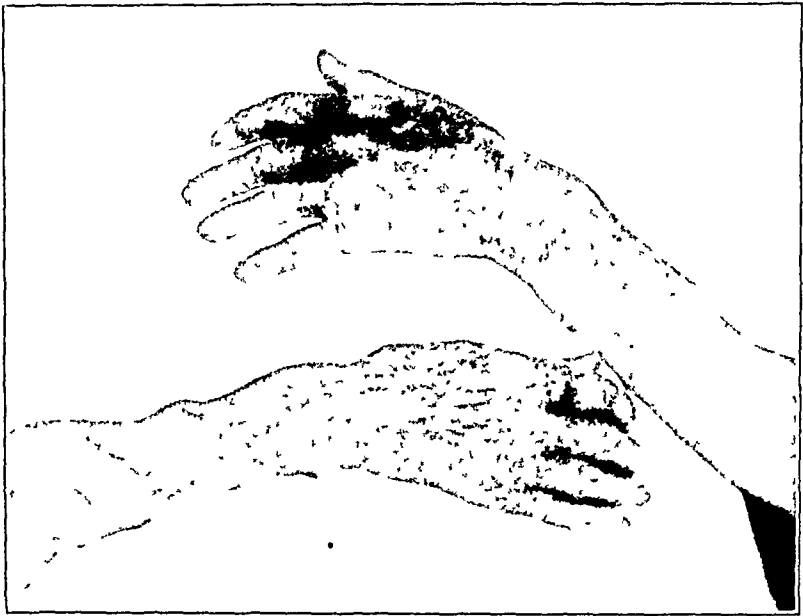


FIG. 5.—Pellagra in an emaciated woman, in the stage of hyperkeratosis and desquamation. (Photograph of the Thompson Pellagra Commission.)

The cutaneous eruption thus presents a variety of pictures in its various stages of evolution. In most cases the appearance is so characteristic that a reliable diagnosis may be made from a single observation. The subsequent developmental course of the eruption furnishes decisive evidence in most of the doubtful cases. In differential diagnosis one may have to consider trichophytoses and other forms of dermatitis due to local infection. These have undoubtedly been mistaken for pellagra at times, as recorded by Roussel. Their localization is hardly ever that of the typical eruption of pellagra. Sunburn may simulate the early stage of pellagrous erythema, but may be distinguished by its regular and

more rapid evolution. Scaly eruptions, which are occasionally observed on the forearms and shins of emaciated or cachectic individuals, may mislead the observer for a time. As a rule, however, the localization as well as the evolution of such eruptions will enable one to differentiate them from the eruption of pellagra.

The manifestations on the part of the digestive tract are variable in character, less constant in occurrence and far less reliable criteria for diagnosis than the cutaneous phenomena. Inflammation of the



FIG. 6.—Pellagra in a young woman in the stage of hyperkeratosis and desquamation. Emaciation is not evident. (Photograph of the Thompson Pellagra Commission.)

mucous membrane of the mouth and pharynx may precede, accompany or follow after the skin eruption. In degree this inflammation may vary from a slight reddening to a condition in which the entire visible mucous membrane is covered with a fibrinous exudate. Intense salivation is an occasional feature. Chronic pellagrins often present an irregularly swollen and fissured tongue. Swallowing may be so painful as to cause the patient to refuse solid food.

A burning sensation in the epigastrium, the pyrosis of pellagra,

is a fairly constant feature. It may precede the cutaneous eruption. Loss of appetite and actual distaste for food are frequently observed, nausea and vomiting only occasionally. In children, diarrhea usually precedes the eruption. In adults, particularly in women and in old men, diarrhea may be absent or may appear only late in the attack. Even in these patients, however, it may become a most alarming feature, the patient passing ten to thirty stools every



FIG. 7.—Pellagra in a child. The legs and feet show extensive eruption (Photograph of the Thompson Pellagra Commission.)

twenty-four hours for several days, with rapidly progressive emaciation and eventual lethal exhaustion. The stools possess a pronounced foul odor, often contain an excess of mucus and sometimes blood. Rectal examination frequently reveals a reddened mucous membrane resembling the redness of the mouth and pharynx. The alimentary disturbances may accompany the skin eruption or may appear, persist or disappear in a way quite independent of the latter. At times an exacerbation of the skin lesions is associated with an

improvement in the alimentary symptoms, and *vice versa*. This is probably mere accident, but some patients state that they always feel better when the eruption has appeared on the hands.

Nervous and mental disturbances are very rare in children but rather common in adults. Symptomatic depression is a frequent early manifestation. Vertigo and actual falling from loss of equilibrium are emphasized as early symptoms by Roussel. In the United States, Singer has found vertigo a prominent early symptom in six of eighteen severe cases. The more pronounced and characteristic nervous manifestations may be considered under two headings, (1) the so-called pellagrous insanity and (2) a peripheral neuritis.

The mental disturbance is either a frank toxic psychosis or one of the usual types of mental disorder varying according to the psychologic make-up of the individual, evidently precipitated by a toxic influence. Mental disturbance is observed in about 40 per cent. of all cases of pellagra, most frequently in women in the age period forty-one to sixty years and in men in the age period twenty-one to forty years. Children are practically exempt. Singer found that about 95 per cent. of the mental disorders appear to be the direct result of the pellagrous intoxication, corresponding to similar mental disturbances in other diseases and not properly to be classed as insanity. Symptomatic depression is the most frequent mental change, and it has been designated as the neurasthenic type. The attitude is that of a more or less hopeless sadness, with a lowering of tone, energy and attention, varying to melancholia, sometimes of a religious type, occasionally with suicidal tendency, to clouding of perception, sense falsifications, stupor and, in the most severe cases, to a syndrome of central neuritis leading to death. In other instances the picture is that of delirium, not essentially different from that of typhoid fever or of pneumonia. In most instances the depression or delirium clears up as the other manifestations of pellagra disappear and physical strength is regained. In about 5 per cent. of the mental cases Singer found a picture corresponding to one or the other of the well-known types of mental disorder, such as manic-depressive, hysteric, dementia precox type or senile dementia. In these cases the attack of pellagra appears to serve as the precipitating cause, which brings out a mental disorder already existing in the patient. During the active pellagrous attack the type of mental disorder may be masked by depression or delirium, but as recovery from pellagra takes place the characteristic features of the individual's preëxisting psychosis become clearly evident. Such patients present actual insanity, but the causation of it is not properly ascribed to pellagra. It would seem, however, that individuals of faulty nervous organization are relatively predisposed to pellagra and that an attack of pellagra tends to make evident the defective nervous organization

of such individuals. Chronic insanity due to pellagra itself, if it occurs at all, is rare.

The peripheral neuritis most frequently manifests itself as a paresis or paralysis of the muscles of the lower extremities. This occurs in children as well as in adults, but is not at all common and may really be due to some accompanying or complicating disease. It resembles an alcoholic neuritis and has been diagnosed as such in some cases. Possibly continued large doses of arsenic may occasionally bear a causal relation to the neuritis.

The temperature is characteristically subnormal in pellagra, varying from 35.5° to 37° C. Frequently it rises rapidly to 39° C. or even higher in the two or three days preceding death.

The pulse-rate is usually high in relation to the temperature and the pulse frequency usually increases sharply along with exacerbation of the other symptoms. The blood-pressure is low.

Duration of the Attack. The usual mild attack of pellagra lasts about four weeks from the appearance of the erythema until the manifestations are no longer evident. In some instances a second attack may supervene before the eruption of the first has entirely vanished, or, without intermission, the hyperkeratosis and desquamation may continue unabated for several weeks or months in exceptional cases. There is a very evident tendency to self-limitation of the attack, but the course and duration are subject to considerable variation and appear to be influenced to some extent by rest, careful feeding and nursing and especially by a diminution in the temperature of the atmosphere. Cooler weather or removal to a cooler climate stands out as perhaps the most definite factor in cutting short the pellagrous attack.

TABLE I.—DISTRIBUTION OF DEATHS IN THE FIRST ATTACK OF PELLAGRA ACCORDING TO YEAR OF ONSET IN SPARTANBURG COUNTY, SOUTH CAROLINA.

Year.	Before 1908.	1908.	1909.	1910.	1911.	1912.	1913.	1914.	Total.
Incident cases . . .	57	20	57	141	234	211	251	209	1180
Deaths	13	2	16	28	33	27	38	30	187
Death-rate per cent.	22.8	10.0	28.1	19.9	14.1	12.8	15.1	14.4	15.8

Death-rate. The death-rate in the first attack in the 1180 recorded pellagrins of Spartanburg County up to 1915 is shown in Table I. The average indicated death-rate, 15.8 per cent., is not very different from that of the later years. It may be regarded as an approximate indication of the death-rate in the first attack of pellagra.

The relationship between death-rate in the initial attack and the race, age and sex of the patients has been studied in these same

statistics. This death-rate in the 1027 white pellagrins was 12 per cent. and in the 153 negroes it was 41.8 per cent. Searcy's earlier report showed a death-rate of 64 per cent. in pellagra among the colored insane. Lavinder's statistics for Mississippi up to 1913 showed a death-rate of 29.2 per cent. in negroes and 11.4 per cent. in white pellagrins. Pellagra may therefore be regarded as distinctly more fatal to the colored race.

In respect to age and sex the Spartanburg County statistics show 14 cases of pellagra at an age of less than two years, 5 white girls, 8 white boys and 1 colored boy, in the total 1180 cases. Of these only one, the colored boy, died in the first attack. Including these infants there were 212 cases in children under twelve years, 99 white boys, 104 white girls, 1 white child of unknown sex, 2 colored girls and 6 colored boys. Of these there died in the initial attack 2 white boys, 3 white girls and 2 colored boys, a total of 7, or 2.5 per cent. In the age period twelve to sixteen years there were only 21 initial attacks of pellagra, 9 in white girls, 11 in white boys and 1 in a colored girl aged fifteen years. Only one of these died in the year of onset, a white girl, aged thirteen years. The low incidence of pellagra in these four years is in marked contrast to the incidence in younger persons of both sexes and to that in older women. In the age period sixteen to twenty years the death-rate in initial attack was 6.7 per cent. in 45 white women, zero in 6 white men, 46.7 per cent. in 15 colored women and 50 per cent. in 2 colored men. The analogous death-rate in each decade after age twenty is shown in Table II. From this table it is evident that pellagra is much more

TABLE II.—DEATH-RATE IN YEAR OF ONSET BY DECADES AFTER AGE TWENTY YEARS.

Decade.	20-29.	30-39.	40-49.	50-59.	60-69.	70-79.	80-89.	Total.
White women . .	4.6	9.8	14.9	31.8	47.6	33.3	..	11.9
White men . . .	16.7	20.0	15.9	24.5	21.7	37.5	100.0*	21.2
Negro women . .	31.0	43.3	63.3	40.0	66.7	..	0.0*	40.2
Negro men . . .	33.3	50.0	0.0	50.0	71.4	..	100.0*	50.2

* Only one case in each instance.

fatal in its initial attack in the negro race and in males, precisely those groups least frequently attacked by the disease in the population studied; furthermore there is a clear indication of increased death-rate with increased age. The benign character of the disease in children is especially noteworthy.

The Interval after the Initial Attack. Subsequent to the initial attack the patient may again become quite fit. There is ordinarily a distinct gain in weight and in some a rather striking gain. The patient frequently refuses to believe that his attack could have been any such serious disease as pellagra. In nearly half the cases,

however, there remains even at this time evidence of depressed vitality, weakness, diminished body weight, diminished or absent menstrual flow in women. As a rule the vast majority of pellagrins improve as colder weather comes on and all but a very few appear quite well in the winter. A few remain weak, cachectic or mentally deranged; rarely one continues with diarrhea and cutaneous eruption into the colder season. These latter usually die in December, January or February. Even in a pellagra focus containing hundreds of cases it is ordinarily impossible to demonstrate the characteristic manifestations of the disease in a single case in mid-winter.

The interval of freedom from pellagra may be prolonged indefinitely so that the patient may be considered to have recovered. This is a common result in institutional outbreaks, where a large number of individuals may be attacked at one time and, subsequently, probably as a result of more liberal dietary and improvement in general hygiene of the institution, the disease may promptly and finally disappear.

In the general population of Spartanburg County, 681 pellagrins who survived the year of onset showed 482 with recurrence and 199 free from recurrence the following year, a recurrence rate of 70.8 per cent. Of those who suffered recurrence in the second year 63 died. Of the survivors 292 were followed through the third year, and of them 228, or 78.1 per cent., had recurrences. Of those who survived attacks in the first, second and third years 78.6 per cent. suffered recurrence in the fourth year and in the fifth year the recurrence rate for those with four previous annual attacks was 76.2 per cent. It would appear that when the habit of recurrence has become established it has a strong tendency to continue. On the other hand those who have escaped from recurrence for one or several years may nevertheless subsequently suffer recurrence. Thus of 137 pellagrins who survived the second year without recurrence, 16 suffered recurrence in the third year, 106 remained free from recurrence and 15 were of uncertain record. Of 62 individuals who had passed two years without recurrence, 11 suffered recurrence in the fourth year of the disease (17.7 per cent.). After three years without recurrence, 13.3 per cent suffered recurrence in the fifth year. Indeed, apparently reliable records in one case indicate a recurrence after nineteen years of freedom from recognizable manifestations of the disease.

It is evident that one should be guarded in stating that any patient has recovered from pellagra. It would appear wiser to speak of the disease as arrested or as quiescent, as is now the rule in tuberculosis.

The Recurrent Attack.—The recurrent attack of pellagra resembles in its clinical features the initial attack. On the average, recurrent attacks appear about two weeks earlier in the season than do the initial attacks of that same year. Recurrences are, on the average, milder than the initial attacks and the death-rate is correspondingly

lower. Thus in the Spartanburg County series the total recorded recurrent attacks number 1053 with 130 deaths, or 12.3 per cent. In the same series the death-rate in initial attack was 15.8 per cent. This observation is contrary to the oft-repeated statement that the prognosis as to life is good in the early stages but bad in the late stages of the disease. It is, however, in accord with the general observation that the severe, fulminant cases of pellagra are more frequent in those places where the disease has recently appeared and are rare in districts where it has been endemic for a long time.

In the Spartanburg County series the total instances of escape from recurrence for a year were 617 and the total number of recurrent attacks 1053, the ratio being approximately 4 to 7. The tendency to recurrence depends to a marked degree upon age and sex. This is shown in Figs. 9 and 10. Of 12 white girls under fifteen years of age, with onset of pellagra in 1911, only 6 were known to suffer recurrence in 1912, 4 in 1913 and 3 in 1914. In

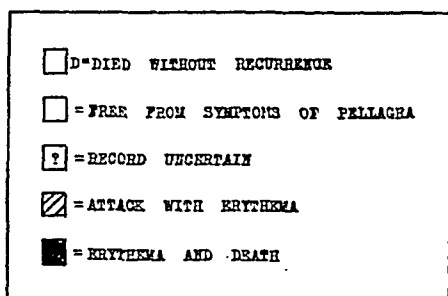


FIG. 8.—Key for interpretation of Figs. 9 and 10. (After Siler, Garrison and MacNeal.)

1914, six remained free from recurrence. Two had passed from observation after 1911 and one had died in 1912 without recurrence of pellagra. The 25 white boys under fifteen years of age with onset of pellagra in the same year show an even more striking recovery rate. Of these 12 escaped recurrence in 1912 while only 8 are known to have suffered recurrence. In 1913 these numbers were 17 and 3 respectively, and in 1914 they were again the same. At the end of four years these 37 children, boys and girls, showed only 6 with known recurrent attack in the fourth year, while 23 escaped recurrence in the fourth year (1914) and 22 were free from signs of the disease in both 1913 and 1914. In the four years there had been only one death in the group, from dysentery, apparently not pellagra. From these and other similar figures it would appear that pellagra is not more serious for children than is measles.

Jobling and Peterson have shown that child pellagrins are of average weight, height and age development until the disease has recurred for some years, when the little pellagrins are somewhat

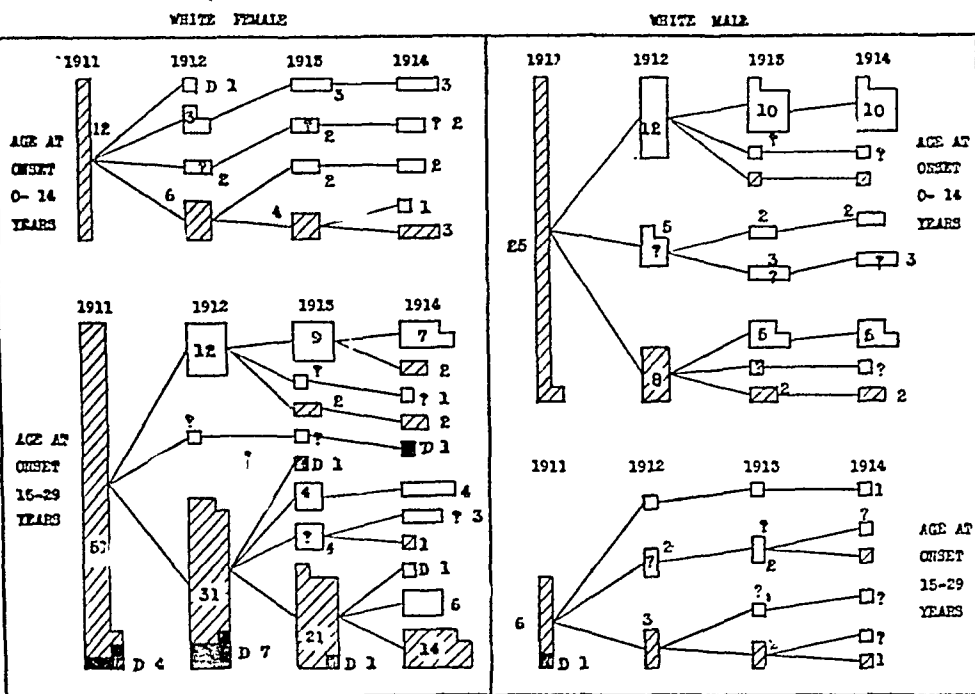


FIG. 9.—Subsequent behavior of white pellagrins of the Spartanburg County series who suffered initial attack in 1911 before attaining the age of thirty years, grouped according to sex and age at onset. Note the absence of deaths in the groups under fifteen years of age and the numerous recoveries in these groups. (After Siler, Garrison and MacNeal.)

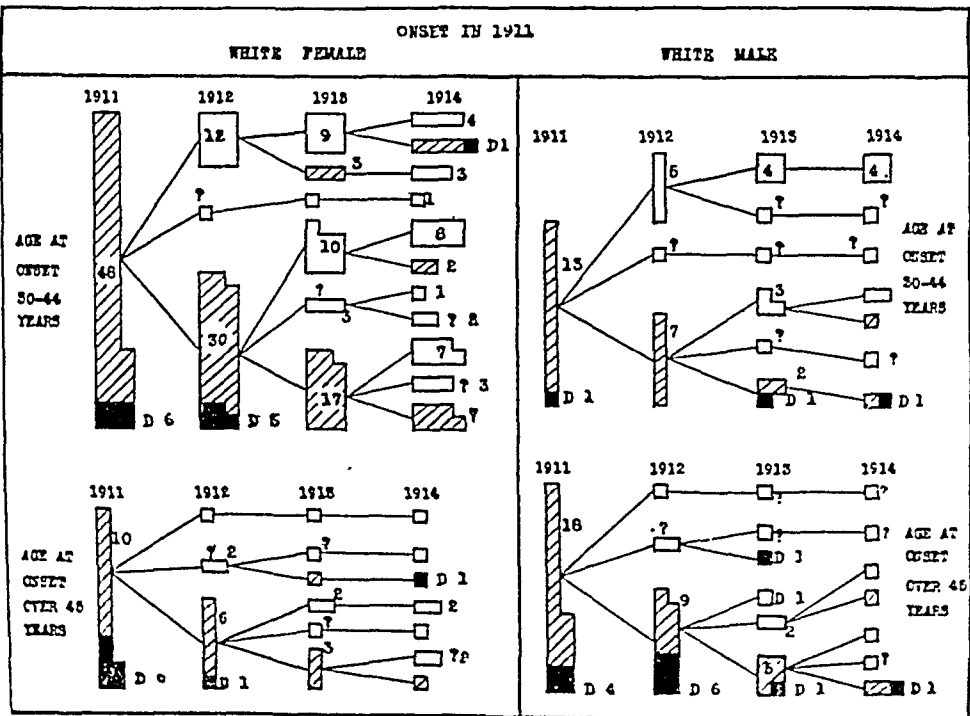


FIG. 10.—Subsequent behavior of white pellagrins of the Spartanburg County series who suffered initial attack in 1911 after attaining the age of thirty years, grouped according to sex and age at onset. Here deaths are more numerous and apparent recoveries less frequent. Note the recurrences after two years of freedom from attack. (After Siler, Garrison and MacNeal.)

below the average. Possibly this retarded development may be due to the pellagra, but there remains also the possibility that these children may be handicapped by some other abnormality, so that they fail to outgrow the disease as does the average normal child, their subnormal development depending upon this complicating abnormality rather than upon the pellagra.

While these children did so well it is interesting to note the behavior of the older pellagrins in the same community, blood relatives of these children, chiefly members of the same families, living in the same houses and eating at the same tables with the children. The women in the age period fifteen to thirty years numbered 55 in 1911. At the end of 1914, 17 were living free from recurrence in the fourth year (1914), 19 suffered recurrence in 1914 and 14 had died of pellagra in the four years. The 7 males in this age group (fifteen to thirty years) are hardly worth discussing. Only 3 were followed in 1914, and of these 2 suffered recurrence and 1 escaped recurrence. The older age groups of both sexes show a similar tendency to recurrence with a death-rate increasing in old age.

Relation to Pregnancy and Childbirth. Pregnant women are relatively less frequently attacked by pellagra, and if the disease appears in them it tends to run a milder course. Thus in our series there were only 20 instances of initial pellagrous attack during pregnancy; 18 recovered, 1 died of pellagra six weeks after parturition and 1 continued in poor health after the child was born in August, 1912, and died of pellagra in September, 1913. Pregnancy bears a similar relationship to recurrent attacks of pellagra. Thus of 79 instances of pregnancy in known pellagrous women, in only 17 instances was a recurrence of pellagra observed during the pregnancy, a recurrence rate of 21.5 per cent. in pregnant women as compared with an annual recurrence rate of 63 per cent. for women in general.

In the months following childbirth women are relatively predisposed to pellagra, both initial and recurrent attacks. In our series 53, or 10.1 per cent., of the pellagrous white women suffered the initial attack of pellagra within six months after the birth of a child. In an analogous manner pellagrous women suffered recurrence of the disease with excessive frequency in the first three months following childbirth, no less than 21, or 24.7 per cent., of the 85 pellagrous white women suffering recurrence in these three months. This rate may be compared with the annual recurrence rate of 63 per cent. by dividing the latter by 4, giving 15.8 per cent. for the average three months period for all women. When the childbirth occurred in the period January to April, inclusive, no less than 50 per cent. of the pellagrous mothers suffered recurrence within three months; when the childbirth occurred in the period September to December all the pellagrous mothers escaped recur-

rence in the following three months. This seasonal relationship should be given attention in the management and care of pregnant women threatened with pellagra.

Pathologic Anatomy. *The Cutaneous Lesions.* Merk has published the most thorough description of the skin lesions as they appear clinically. Unfortunately his work did not include histologic studies. Griffini appears to have been the first to describe the microscopic appearance of the skin. In the desquamative stage he observed a hypertrophic horny layer, with evidence of abundant scaling and excessive productivity in the rete Malpighii. In another case, in the stage of "anemia," he found sclerosis of the bloodvessels of the cutis, more particularly of the papillæ. A third case was examined at the atrophic stage. In this one Griffini found sclerosis of the deeper cutaneous vessels and of the connective tissue of the corium, a frank atrophy of the horny layer and little reproductive activity of the rete Malpighii. The sweat-glands, hair follicles and sebaceous glands seemed not to be abnormal.

P. Raymond studied the skin from the back of the hand of a chronic pellagrin in the atrophic stage. The epidermis as a whole was thinned but the horny layer was thickened absolutely as well as relatively; the papillæ were smoothed out. The horny layer and the rete Malpighii were of equal thickness and the former showed numerous clefts, indicating active desquamation. Hyperkeratosis was a most prominent feature. The stratum granulosum was composed of thin, elongated cells in which eleidin granules could not be distinguished. The rete was atrophic, showing reduction in both number and size of cells. Many of the nuclei had undergone a vesicular degeneration, which Raymond considered to be evidence of irritation in response to vascular dilatation in the corium. The basal cells contained abundant pigment. The papillæ had vanished entirely and the boundary between the ectoderm and the mesodermal layer was represented only by a slightly toothed band. In the corium there were large vascular tufts, the large volume of which contrasted sharply with the atrophic epidermis. The hair follicles, sweat-glands and particularly the nerves were unchanged. The elastic and collagenous fibers appeared normal except for moderate thickening of the latter. In summary, Raymond designates hyperkeratosis and atrophy of the rete as the essential cutaneous changes of pellagra.

Babes and Sion appear to have studied the skin in various stages of the disease. They mention the various features of pellagrous skin lesions, including secondary infections which take place, but these descriptions are inferior to Raymond's in respect to clearness. Babes and Sion mention a moderate diminution in the myelin of the cutaneous nerves as well as the presence of rod-like structures in the corium, suggesting bacteria. They found sebaceous glands containing bacterial colonies and surrounded by granulation tissue,

in which hyperplastic endothelial cells and plasma cells were abundant.

Ormsby and Singer, after study of a large number of sections of pellagrous skin, designate the general picture as that of an angio-neurotic process resembling that seen in multiform erythema. They observed thickening of the horny layer, the stratum granulosum and rete being practically normal; edema and cell infiltration

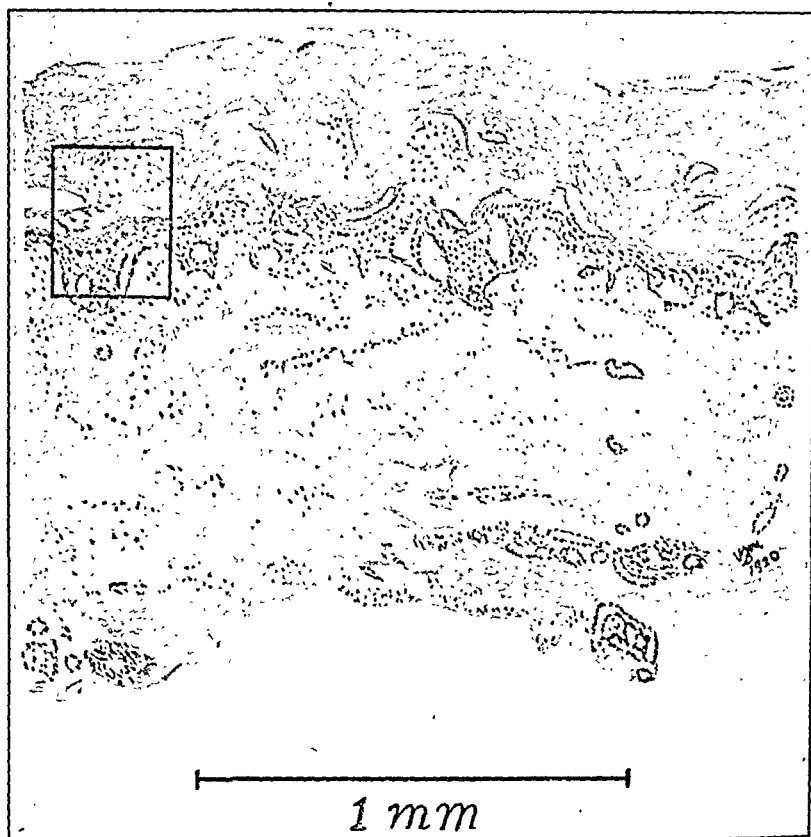


FIG. 11.—Section of skin with mild pellagrous eruption in the stage of hyperkeratosis from a woman aged twenty-nine years; stained with hematoxylin and eosin and drawn with aid of the camera lucida. The horny layer is greatly thickened and shows active desquamation with scattered areas of parakeratosis. There is edema of the corium, especially of the papillary part.

of the superficial part of the corium, especially the pars papillaris. Upon study with the high power the hyperkeratosis was seen to be well marked, with areas of parakeratosis here and there. Many pigment granules were present. The rete was practically normal except in places where its integrity was interfered with by infiltrating cells. In the papillary layer cellular infiltration was quite marked, particularly in the vicinity of bloodvessels. The collagen showed

edematous changes. Deeper parts of the corium appeared normal. No microörganisms were found.

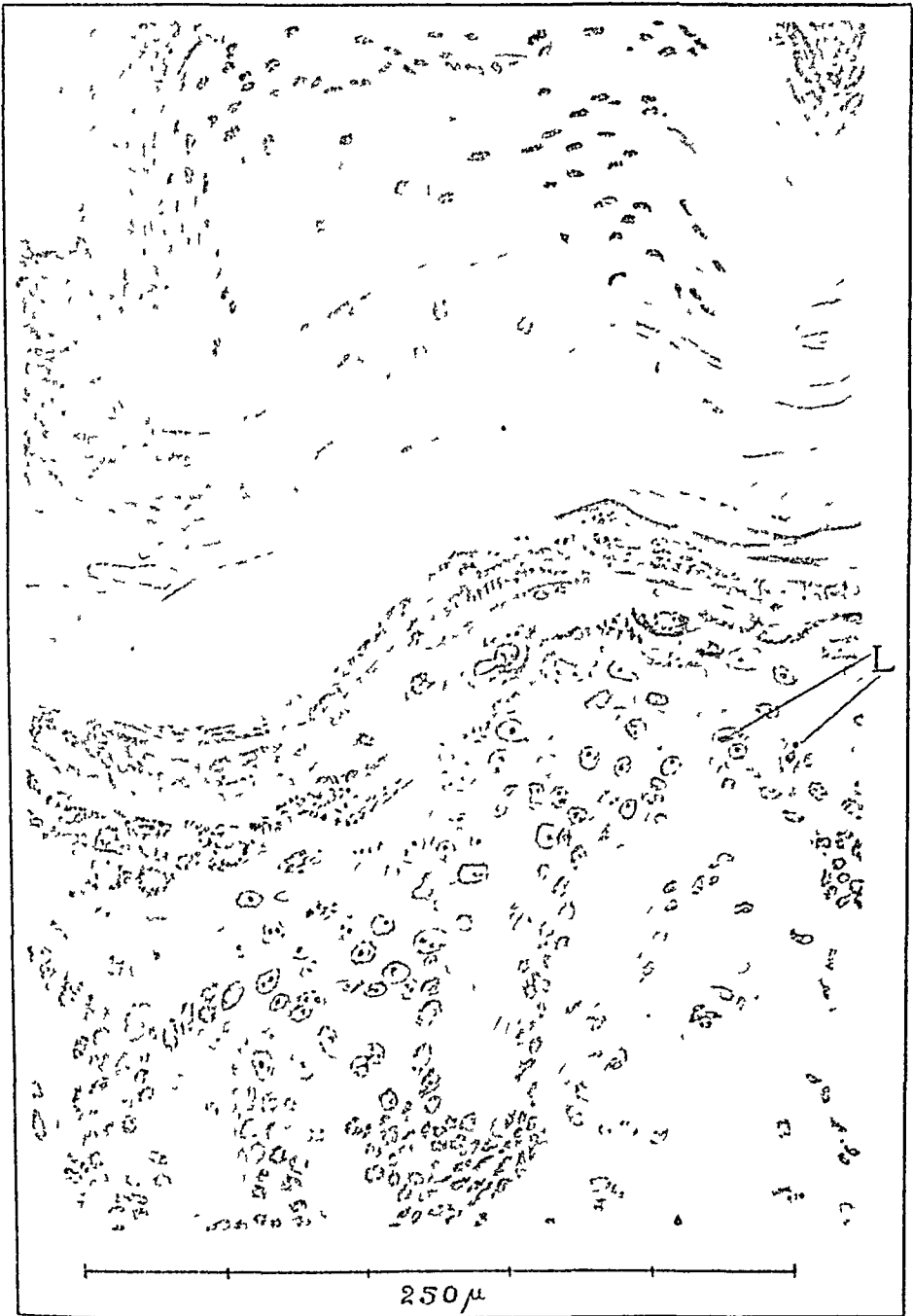


FIG. 12.—A portion of the same section, the location of which is indicated by the black outline in Fig. 11, more highly magnified; camera lucida projection, Zeiss obj. 4 mm., oc. 4. Active desquamation is indicated by the clefts in the horny layer and parakeratosis by the many nuclei in this layer. The stratum lucidum contains numerous brown pigment granules. The regularity of the stratum granulosum is disturbed and the lymph canalicular system of the rete Malpighi is moderately distended by edema. Increase of wandering cells is only slight. At L are leukocytes.

An adequate description of the cutaneous lesions of pellagra will require a consideration of all the various stages of the eruption, with a correlation of the gross and microscopic appearances. One may sometimes find several stages of the eruption represented in different areas in one individual at the same time. From the description reviewed above, supplemented by rather limited study of microscopic preparations, it seems to me proper to recognize an early stage, in which vascular injection and edema of the corium are prominent features, with which is associated a diffuse infiltration with wandering cells, more abundant in the more severe lesions. These cells are found particularly in the papillæ, but also wander up into the rete. Subsequently there is added edema and hyperplasia of the rete, hyperkeratosis with spots of parakeratosis, large and abundant in the more severe lesions. Perhaps the most severe type of this stage is represented by the bleb, which becomes secondarily infected and purulent, ulcerated. In the milder forms the vascular injection diminishes. A little later, hyperpigmentation appears, especially in the rete. Hyperkeratosis continues and gradually the hyperpigmentation becomes more superficial, occupying the stratum lucidum and deepest strata of the horny layer. The relationship between congestion, edema, cellular infiltration, hyperkeratosis, parakeratosis and pigmentation is subject to wide variations, depending in part upon individual peculiarities (greater pigmentation in brunettes) and in part upon the rapidity of evolution and the severity of the eruption. An exaggeration of the edema leads to formation of blebs and ulcers, eventually purulent. Less acutely severe eruptions are relatively dry and in these the hyperkeratosis and pigmentation tend to be exaggerated. After exfoliation of the thickened horny layer the remaining epidermis is abnormally thin and the papillæ relatively smoothed out. Complete restitution may occur after a few weeks, but in many instances after prolonged severe eruption and especially after repeated severe eruptions the epidermis remains permanently thin, atrophic, with diminutive papillæ beneath it and a fibrous corium of increased density and deficient in smaller bloodvessels. There seems to be no characteristic alteration of the nerves, sweat-glands, sebaceous glands or hair follicles, or at any rate the evidence of such changes so far brought to light does not establish them as a part of the uncomplicated cutaneous lesion of pellagra. The cutaneous eruption suggests the action of a toxic irritant brought by the blood or lymph, to which the epidermis of the region is particularly sensitive. It is further suggested that this toxic substance may be relatively inactive until it has been changed at the site of the lesion by peculiar ferments of the epithelial cells or possibly by the accessory influence of diffuse or direct sunlight.

The Nervous Lesions. These also require to be considered in relation to the stage of the disease. The earlier observations of

Tuczek would seem to deal rather with the late after-effects of numerous attacks of pellagra if not actually with results of other complicating diseases. More recent studies, particularly those of Mott and of Singer, have brought into prominence the structural changes in the ganglion cells themselves throughout the brain, spinal cord and spinal ganglia. In a rapidly fatal initial attack of

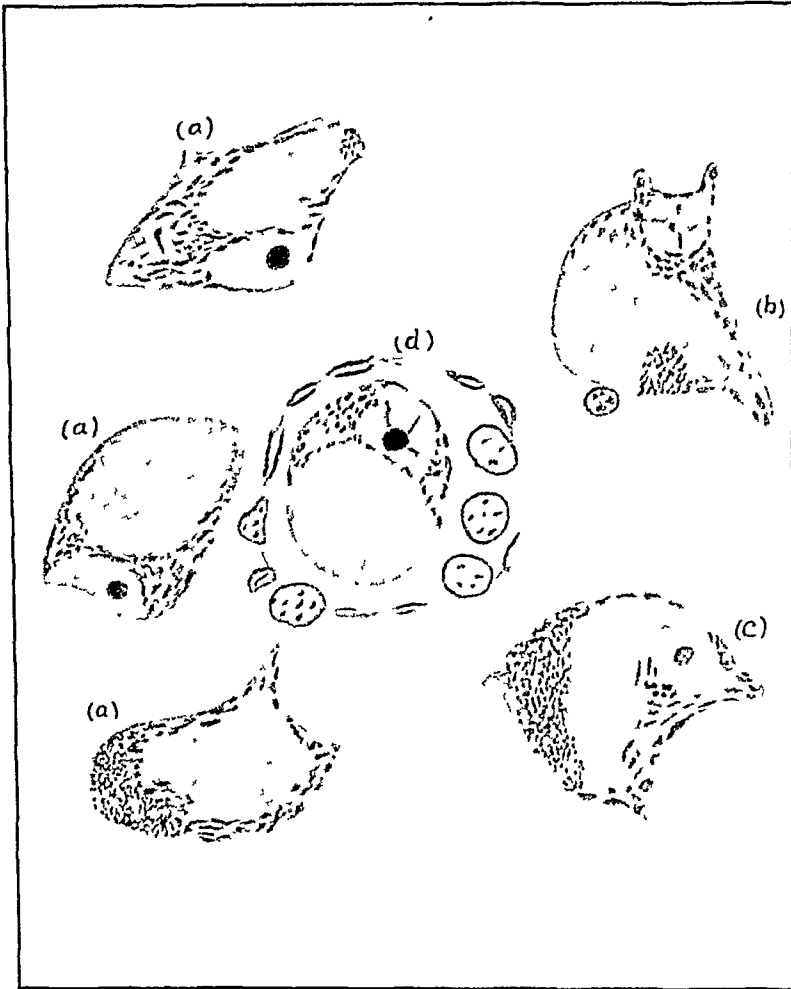


FIG. 13.—Nerve cells showing chromatolysis and pigmentary changes. (a) From Clarke's column; (b) from anterior central convolution; (c) from anterior cornu in cervical region; (d) from posterior root ganglion. From a woman, aged forty-three years, dying in the initial attack. (After Singer.)

pellagra, Singer found the most pronounced changes in the Betz motor ganglion cells of the cerebrum and in the cells of Clarke's column in the cord. Fiber degeneration was found diffusely scattered throughout the white matter, not especially involving the pyramidal tracts and not abundant in any tract. Degenerated fibers were also found in both the anterior and posterior spinal roots. The glia cells were perhaps increased around some of the larger

bloodvessels and in places the cerebral vessels showed some increase of adventitial nuclei, but no infiltration of the perivascular sheaths, a striking contrast to the pictures seen in syphilis and in trypanosomiasis. In more chronic cases the increase in glia cells about the bloodvessels was more definite and quite marked in some instances, and the vessels themselves were thickened. The nerve lesions, like the cutaneous changes, indicate the action of a diffusely distributed toxic substance in solution in the blood and lymph, for which the nerve cells possess, a special susceptibility, rather than a formed, more definitely localized infectious agent present within the nervous tissues.

The Lesions of the Digestive Tract. In the alimentary tract also the lesions vary with the stage of the acute attack and represent only after-effects in the interval between attacks. During life the inflammatory hyperemia of the mouth, pharynx and of the rectum are often prominent features of the active pellagrous attack. Autopsy at this stage nearly always shows inflammation throughout the intestine, patchy in distribution. Strips of hyperemic intestine several feet in length alternate with strips fairly normal in appearance. The duodenum, lower ileum, caput coli and rectum commonly show the most severe changes. In the earlier lesions there is vascular engorgement, hyperplasia of the lymphoid tissue, edema and infiltration of the mucosa with wandering cells. In later lesions, possibly as a result of secondary infection, moderately dense collections of wandering cells extend from the epithelial surface into the submucosa and along the vessel sheaths even into the muscular coats. Loss of superficial epithelium is evidently extensive, for even in the milder lesions one finds numerous mitoses in the crypts and, in the older, more severe lesions the glands are deficient in number and quite variable in form and size. Ulceration commonly occurs in the lower ileum, caput coli and rectum, and these ulcers, which are small, round and superficial, nevertheless heal only slowly, so that they may be seen at autopsy after the diffuse intestinal inflammation is no longer evident.

The intestinal lesions of pellagra are least well understood. Some authorities (Roussel) regard them as entirely trophic and dependent upon antecedent changes in the nerves. Others regard them as an expression of direct toxic action on the intestinal wall by the essential poison of pellagra during its absorption. Doubtless the normal intestinal microorganisms also play a part, particularly after ulceration has occurred. A clear understanding of the intestinal lesions will doubtless have to await a better understanding of the etiology of pellagra itself.

Pathologic Chemistry. Myers and Fine found the gastric juice of pellagrins often deficient in hydrochloric acid and not infrequently in pepsin also. The feces contain, as a rule, a markedly abnormal excess of indol and skatol. The urine commonly shows a

trace of albumin and a few tube casts and in most cases a distinct test for indican. At times indican is present in enormous amount. These findings all point to a gastro-intestinal derangement and profound bacterial decomposition in the intestine. Metabolism studies on pellagrins have shown that these patients possess normal ability to utilize the food principles. In fact the utilization was surprisingly high, considering the evidence of local gastro-intestinal derangement.

Bacteriology. The work of Tizzoni and his associates, who have isolated an organism from the blood which they regard as the cause of pellagra, may probably be dismissed as unreliable. The intestinal flora is certainly profoundly altered in pellagra. There is a large increase in the variety of microbes present in the feces as compared with the normal as well as a disturbance in the numerical relationships of the normal types. Further investigations in this field of work are much to be desired.

Diagnosis. The diagnosis of pellagra has to be made by observation of the symptoms and signs presented by the patient, and this diagnosis may be supported by demonstration of the typical anatomic changes in the tissues. Accessory facts may be utilized to some extent. Of these, perhaps the most important is a history of having lived in a pellagrous district. Some authors attach great importance to a history of having eaten maize, even going so far as to exclude pellagra absolutely if maize has not been eaten (Roussel) or even to assume that all persons who habitually eat maize actually suffer from pellagrous intoxication in a mild form. These conceptions are not in accord with observations on pellagra in the United States. Some authors appear to attach considerable importance to emaciation and physical weakness as evidence of pellagra, but these manifestations are common to so many pathologic conditions that comment upon their diagnostic value is superfluous.

Among the signs and symptoms, only the typical cutaneous eruption on the backs of the hands warrants a definite diagnosis of pellagra. This eruption bears the same relation to the diagnosis of pellagra as does the eruption of smallpox or measles to the diagnosis of those diseases. In the recognition of the pellagrous eruption, its localization on the backs of the hands, approximate bilateral symmetry, sudden appearance as an erythema, gradual evolution to hyperkeratosis, with or without hyperpigmentation, the subsequent desquamation and final restitution are important. A dermatitis due to molds may simulate this eruption in appearance, but such a dermatitis usually occurs elsewhere than on the backs of the hands. Roussel, however, mentions cases in which the differential diagnosis was finally made only by the microscopic demonstration of mycelial threads in lesions on the backs of the hands. The beginning and developmental course of a mold derma-

titis is usually different also, so that continued observation may alone suffice for its recognition.

A tentative diagnosis of pellagra is often justified without observation of the eruption. Certainly the disease is usually still present after the acute attack and the eruption have disappeared and there is abundant evidence that the patient suffers from the disease in the absence of the eruption. However, such a tentative diagnosis should be abandoned if the patient does not subsequently present the eruption or confess to its earlier presence.

Prophylaxis. The practical prevention of pellagra has to be based upon a knowledge of etiology. The measures may be grouped in two classes: (1) Those measures which enhance the individual resistance to the disease, and (2) those which diminish or exclude the opportunity for the causative factor or factors to attack the individual. First, in regard to individual resistance: it is evident that even in its endemic centers pellagra attacks only a small proportion of the population at any one time. Those who are physically vigorous escape to a very large extent and therefore the maintenance of robust physical vigor is an excellent insurance against pellagra. The nature of human existence, however, is such that in every natural community of families there will be some tender young children, some children occasionally sick with measles, whooping-cough or gastro-intestinal derangement, some women in the puerperium and some old people in the decline of life when robust vigor naturally wanes. Therefore, although the maintenance of individual resistance at a high level offers much, it nevertheless has its limitations. In regard to the second class of measures, which diminish the opportunity for the cause to reach the individual, opinion is much less settled. Most effective is distance from persons suffering from the disease. When pellagra has prevailed among the general population new cases may be expected to continue to appear. In the United States the disease numbers its victims by the thousands every year in some states while in others it is either wholly unknown or is recognized as a rare disease of transient visitors from pellagrous districts. Even in its endemic areas, large districts remain relatively free from the disease while in other parts from 5 to 10 per cent. of the people are pellagrins. Avoidance of the endemic centers becomes, therefore, an evident means of avoiding pellagra. However, even in the small villages most severely afflicted, those people who live farther away than next door from the residence of a pellagrin are less liable to contract the disease than those who live next door to or in the same house with such sick persons.

Sanitary disposal of the human wastes of a community would appear to be one of the most important factors in preventing the occurrence of new cases of pellagra. Physical equipment such as sewers, a piped water supply and screens are evidently important,

but sanitary instruction, and especially adequate inspection service to insure the proper use of the equipment, must not be neglected. Lunatic asylums, provided throughout with the most approved sanitary appliances, still have their "untidy wards."

General improvement in nutrition, and particularly the liberal consumption of milk and of wholesome, fresh meat, certainly plays an important part in preventing pellagra, not alone among those who have not yet contracted the disease but also in preventing recurrences in those already affected by it. It is probable that such foods act by enhancing the general vigor and thus increasing resistance of the individual to the disease, but many investigators believe that these foods have a more definitely specific action by relieving a supposed specific deficiency or supplying a necessary vitamine in the diet.

Treatment. The treatment of pellagra offers two phases for consideration: (1) The management of the case during the acute attack of the disease, and (2) the management of the patient after recovery from the attack. As we have seen, recovery from the attack occurs in about 85 per cent. of instances. In fact, about half the attacks do not cause the patient to go to bed and the vast majority run their course to recovery without any definite treatment. In those who do become bedridden the death-rate is fairly high.

Bearing in mind, therefore, that the attack tends to self-limitation the indications are for supportive and symptomatic treatment. A comfortable bed in a clean, pleasant and moderately cool room, with a competent, interested and sympathetic nurse, almost ensure recovery. The lips, mouth, teeth and pharynx should be kept scrupulously clean. Irritation of the eruption is lessened by bandaging with an ointment of zinc oxide, lanolin and vaselin. The diet should be liberal and should include milk as the principal element. Every effort should be made to encourage the appetite, but over-feeding to the point of distaste or nausea is dangerous. In severe cases food may sometimes be refused entirely for as long as three days, with subsequent return of appetite and eventual recovery. Pellagrins are very susceptible to suggestion and the presence of recovered patients has a real therapeutic value. Conversely, a pellagrin, surrounded by friends or by nurses who regard the disease as horrible and necessarily fatal, usually dies. Probably the psychical state influences directly the nutrition and indirectly the outcome of the attack.

Pustules, fissures, ulcers and extensive sloughs of the skin require mild antiseptic wet dressings. The diarrhea had best not be interfered with, and it is not a contra-indication to a liberal milk diet. Peripheral neuritis and paresis require massage, passive movements and elevation of the bed-clothing from the feet in chronic bedridden cases. Mental derangement should be expected in all severe cases, and it requires intelligent, sympathetic treatment.

Physical restraint usually aggravates the difficulty. Of the hypnotics, probably chloral is most effective and least objectionable. Morphin is not recommended. Mental cases require vigilance, for there is a real suicidal tendency in some. The noisy delirium of these patients makes their treatment in a general hospital very difficult.

Complicating disorders should be carefully looked for. Often their importance quite overshadows that of the pellagra itself. In a tuberculous pellagrini treatment of the tuberculosis is the pressing indication. Chronic alcoholism and its sequelæ, and, in women, pelvic disease, are common complications of pellagra and require their special consideration. In institutional pellagra, undernourishment from prolonged lack of adequate food is common, and it is one of the most easily corrected complications.

After recovery from the attack every effort should be made to prevent recurrence by increasing the general resistance of the patient and by adequate treatment of any debilitating disorder, particularly those just mentioned. Relief from overwork, administration of tonic drugs and especially removal to a cooler climate are to be recommended. Particular efforts should be made to retain the resistance and the nutrition of the patient at a high level during the spring and early summer of the following year because of the danger of recurrence at this time. Public charity may do much to better the resistance of poverty-stricken pellagrins, but it sometimes happens that the particular handicap of the patient cannot thus be relieved, and this is especially true of those pellagrins who are already in comfortable financial circumstances. Such patients may require a careful study of their general condition and a careful regulation of their lives for a period of several years.

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NOTE.—Numerous references to earlier articles by these same authors and by other authors will be found in the papers cited above.

THE ABSENCE OF PANCREATIC SECRETIONS IN SPRUE AND THE EMPLOYMENT OF PANCREATIC EXTRACT IN THE TREATMENT OF THIS DISEASE.

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OUR ideas of sprue as a clinical entity date from the works of Manson, Vander Burg and Fayrer in the '80s, although it has been recognized since 1737, and Hillary clearly defined it in 1766. Manson described it as a disease of the tropics, characterized by "a peculiarly inflamed, superficially ulcerated, exceedingly sensitive

condition of the tongue and mouth; great wasting and anemia; pale, copious and often loose, frequent and frothy, fermenting stools; very generally by more or less diarrhea, and also by a marked tendency to relapse." Castellani and Chalmers, in the last edition of their *Manual of Tropical Medicine*, 1919, define it as follows: "Sprue is a chronic catarrhal inflammation of the alimentary canal of unknown cause, characterized by a peculiar ulcerative condition of the tongue and mouth and by the passage of large, pale, smooth motions, the symptoms waxing and waning periodically." The disease is endemic in certain parts of Asia, affecting primarily the Europeans, though the natives are not immune, and it is widely distributed all through the tropics (under various names, such as Ceylon sore-mouth, psilosis, diarrhea alba, aphthæ tropicæ, etc.), while ever increasing communication between tropical and temperate countries has resulted in more and more cases being seen in Europe and in North America. Recently renewed interest has been aroused in the United States of America in the subject of sprue by the work of Wood, who calls attention to the fact that a certain number of cases regarded as atypical pellagra, and seen in our Southern States, are in reality mild but definite cases of sprue. Unquestionably, living in hot, humid climates, previous wasting diseases and improper diet render one more susceptible to the disease, but the definite etiologic factor or factors have not as yet been absolutely determined, although, at the present writing many authorities, probably the majority, are in favor of regarding the disease as due to a monilium infection. Kohlbrugge's theory that the disease is due to infection by *Monilium* or *Oidium albicans* has been supported by Bahr and others, though Castellani has described several other varieties of monilium in the stools of patients with sprue, while Ashford believes that it is not *Monilium albicans* but another parasite—*Monilium psilosis*—that is the cause of the infection, and he and others believe that they have definitely proved this by immunologic and vaccine studies, by agglutination and complement-fixation tests and by feeding experiments on monkeys with reproduction of the disease. Dold and others, however, believe that "an excessive acid- and gas-producing microbe is an essential factor in the disease," and "that in various countries different kinds of organisms having the same pathologic effects will be found causing this disturbance." In this connection it may be mentioned that Castellani has reported a number of cases markedly improved by the administration of large doses of bicarbonate of soda, while certain writers believe that the disease is produced by certain cocci or protozoa. Unquestionably the two theories most supported are either that the disease is in reality a moniliasis, due to one or several varieties of this fungus or that it is due to dietetic errors and probably represents a real deficiency disease, as McCarrison has especially suggested,

As one would expect from the symptoms, most authorities lay special stress upon the *pathologic anatomy* of the disease as it affects the *digestive tract*, although Manson has insisted that while certain of the findings undoubtedly represent the *primary* lesions due to the disease, others unquestionably represent the effect of the *secondary* long-lasting tissue starvation due to the disease and are very similar in character to the intestinal findings in famine patients. Certainly in all severe, chronic cases there is "an irreparable destruction of the mucous membrane of the alimentary canal both of the secreting and absorbing tissues" (Manson), all leading to the thinned intestine with diaphanous wall, with absence or marked diminution of villi and glands, congestion, ulceration and erosion, and sometimes cicatricial replacement, which are obviously basic causes of the digestive symptoms which dominate the picture and which are due to the effect of such a pathologic condition upon the digestion and assimilation. Microscopically we meet with small-cell infiltration, a smooth and atrophic mucous membrane, small follicular ulcers, notably in the lower ileum, the primary lesions, according to Castellani, being beneath the epithelium in both the tongue and intestine, the former producing the peculiar mouth picture so characteristic of the disease.

Certainly, whatever the primary causes, digestion and absorption are very markedly affected by the pathologic conditions produced, and the acids produced in such abundance must markedly disturb digestion, notably the emulsification and digestion of the fats, so that there is often 40 to 50 per cent. of undigested fat in the stools. Certain authorities believe also that the changes that have been described in the liver leading finally to atrophy lessen so markedly the detoxifying properties of this organ as to add a definite picture of intestinal toxemia to the other symptoms of the disease.

Strange to say, after a very careful searching of the literature we have been unable to find in detail any careful notes as to the microscopic changes in the *pancreas* in sprue; most authors, such as Manson and Schmidt, do not mention it at all in their description of the pathology of the disease; others content themselves with stating that the pancreas is normal, inflamed or cirrhotic, this probably based on macroscopic findings, as no note is made of the microscopic examination of this organ.

In 1916 we published¹ the results of our quantitative studies of the pancreatic ferments in a case of sprue sent to us from Porto Rico, and finding that all three ferments—trypsin, lipase and diastase—were absent, administered pancreatin to the patient in addition, of course, to the recognized treatment of this disease, and were very much struck with the remarkable improvement that took place, an improvement coincident with the administration of

¹ Johns Hopkins Hosp. Bull., October, 1916, No. 308.

pancreatic extract and stopping with a recurrence of the symptoms shortly after the pancreatic extract was withdrawn, so that for the patient to remain perfectly well clinically it was essential to administer the extract constantly. While many had suggested that there was a diminution or absence of pancreatic ferments, as obviously suggested by the character of the stools, notably the large excess of undigested fat therein, we believe that ours was the first case in which this was definitely proved by very careful and repeated estimations of these ferments.

Since our first case we have had the opportunity of studying 4 other cases—thus making 5 in all—2 coming to us from Porto Rico and 3 from the Philippines. All had been diagnosed as sprue by experts in this disease and were of long duration, and in none had the symptoms been present for less than one year. In each case the symptoms were typical: gradual onset, sore-mouth, diarrhea very marked in the morning, indigestion, increasing loss of weight, diminished appetite in 4 of the cases, abdominal discomfort, much gas, a marked tendency to ballooning of the abdomen, which in one of the cases was of the maximum degree, often coming on with no apparent cause and producing great discomfort; the tendency to relapse had been noted in each of the cases. The stools were characteristically frequent, voluminous, frothy, gray in 4 cases, yellow in one, with mucus, many bacteria, acid reaction and marked excess of fat; we did not, however, make very careful studies of the stools for monilium or other intestinal parasites. By proper methods bile pigments could be demonstrated in the stool in every case, and the gray color, therefore, was not due to lack of bile but was probably caused by leukourobilin—a not at all improbable transformation in the absence of pancreatic secretions—although Castellani believes that in certain cases this color is due to various bacteria, as, for instance, *Bacillus alba*faciens.

Our *quantitative* estimation of the pancreatic ferments was made from studies of the stool in all our cases and from the duodenal contents obtained with the Einhorn bucket in 3 cases. These quantitative estimations of the ferments in the stool were made once in 1 case, twice in 3 cases and five times in 1 case, there being an interval of nearly a year between the third and fourth and fourth and fifth estimations. The methods employed were those previously described by us;² for the diastase we used a modification of the Wohlgemuth method, for the trypsin the Fuld casein method, for the lipase 1 per cent. monobutyrin, while the same methods, with slight modifications in regard to dilution, were used in estimating the ferments in the duodenal contents. In both our 5 cases, both in the original experiments and in the repetitions of the tests, whether with the stool, which we regard as more exact quantitatively, or

² Johns Hopkins Hosp. Bull., September, 1912, No. 259; July, 1914, No. 281 and elsewhere.

with the duodenal contents, none of the pancreatic ferments was found, or in such minimal amounts as to fall within the limits of error. Thus in the case of diastase we had previously estimated the low normal amount of this ferment in the stool after the method which we had described and which was based on the study of a large number of normal cases.³ This low normal amount we found to be 600 starch gram units, but in each of our cases of sprue the reading showed less than 12 units, this being our tube of greatest dilution, as we regard it as impossible to draw any conclusions as to lesser amounts than this. All these findings are so striking that we feel that it is beyond question that certain of the chronic cases of sprue are associated with a complete absence of pancreatic secretion, and this must play a role in the production of the symptoms, although, of course, our series is far too small to deduce from it any general conclusions. We should have liked to have estimated quantitatively the intestinal ferments in these cases as well, but the inherent difficulties are so great and the readings obtained so open to criticism that this procedure was not carried out. Nevertheless, if one can judge from the pathologic findings there must be an enormous diminution in the intestinal ferments, and the effect of the absence or diminution of certain of these, such as erepsin, enterokinase, the inverting ferments, possibly the duodenal hormone which brings about pancreatic secretion, and, at the same time, the disturbances in the chemistry of the chyme, notably as regards reaction and character of the bile, must play an enormous role, not only *per se*, but in the effect of these variations from the normal upon the secretion of the pancreatic juice. Whether this absence represents organic changes in the gland, whether it is due to functional disturbance or to destruction or changes due to lack of activation of the ferments after they have reached the duodenum, are obviously questions which we are unable to answer. In regard to the gastric contents of our 5 cases, 1 showed hyperacidity, 2 subacidity, 2 achlorhydria, but in the case of these last two groups a return to a practically normal gastric contents was coincident with the very marked clinical improvement noted; the one case that showed no improvement under treatment was that associated with hyperchlorhydria. Both the cases with achlorhydria showed a return of acid very shortly after they began to show improvement in symptoms. Castellani has noted that the test-meal may show diminished hydrochloric acid and pepsin, while Van der Scheer found no special changes in either gastric secretion or gastric motility in his 13 cases. Certainly, in our small experience the gastric picture is neither constant nor significant.

In regard to *treatment*, the usual therapeutic measures in vogue—encouragement, absolute rest, fresh air, sunshine and a very carefully selected diet—were used in all cases. As regards diet, in the 4 of

³ Johns Hopkins Hosp. Bull., July, 1914, No. 281.

our cases that did so well a diet beginning with buttermilk, which we chose in place of ordinary milk because these cases showed deficiency of acid in the gastric juice, then gradually adding egg, zwieback, bread-and-milk and other simple, soft and liquid foods, including fruit juice and purée of fruits, was so well borne that there was no need of trying other special diets. All these cases had obviously tried change of climate but none had been given monilia vaccines. In the fifth case—the one that showed no improvement whatsoever on this diet—we tried fruit diet and meat diet, with special attention to strawberries in the former, but neither was well borne; in fact, all diets seemed to be equally poorly borne, and the only means of helping him seemed to be courses of neosalvarsan intravenously, and this produced a marked temporary improvement, as it had done previously in his case in the Philippines. In the cases with sub-acidity or anacidity we gave hydrochloric acid until their gastric contents gave practically normal figures. In the case with excessive hydrochloric acid we used sodium bicarbonate in large amount, but, if anything, this seemed to add to his distention and his discomfort. We did not try yellow santonin, so strongly recommended by Begg, nor did we think appendicostomy and irrigation, as suggested by Van der Scheer, advisable or justifiable.

In all of our cases, based on our finding of the complete absence of pancreatic secretion, we gave large doses of pancreatin or some form of pancreatic extract, 5 to 10 grains, with 20 to 40 grains of calcium carbonate or calcium lactate three times daily, two hours after the larger feedings; in 4 of the cases the results were really so remarkable, the treatment seemed so markedly efficacious and the improvement so rapid as to make each one feel that it was definitely due to their being supplied with the ferments in which they were deficient. This improvement persisted as long as the treatment continued; 3 of the 4 cases were lost sight of in three or four months after the treatment started, but they seemed clinically much better. The fourth case—a patient who had moved from Porto Rico to Virginia and was constantly near enough to be seen every few months—continued well so long as she took the pancreatin; in fact, while on the treatment she was clinically absolutely free of all signs and symptoms of the disease and looked and seemed absolutely well. On the other hand, if she stops the pancreatin for a few days the tongue becomes sensitive and sometimes red, she developed a morning diarrhea and the abdomen feels distended and uncomfortable, and the stool becomes more voluminous and unquestionably shows increasing fermentation. But all these symptoms rapidly disappear with the readministration of the ferment. This case has been carefully studied a number of times in the years that she has been under our observation, but the stool still always shows a complete absence of secretion from the pancreas, and it is quite obvious that, in her case at least, health is absolutely dependent upon the regular and

constant administration of pancreatin. The fifth case showed absolutely no benefit from the use of pancreatin; his was the longest history—over three years—although on admission he apparently was by no means so ill as our first case—the one who has been studied the most carefully of our series, though he was definitely more ill clinically than the other three. We have felt in his case that the destruction of glandular tissue was so great that there must have been such reduction in intestinal ferments, in addition to his complete pancreatic insufficiency, that he was unable to either digest or assimilate more than the very minimum amount of food, and, in this case, we should have liked to have tried intestinal ferments and possibly liver extract in addition to what we were giving—whether they would have produced any benefit is obviously problematical.

These cases are far too few in number to justify us in drawing definite general conclusions in regard to the pancreatic secretions in sprue, but we do feel that they add something to our knowledge of the secretory disturbances met with in this disease and are worth recording, both from the point of view of pathology and of treatment. The careful study of these cases leads one to certain queries anent this disease: Is sprue one or several diseases? Are the major portion of the symptoms due to the primary lesion or are many of them much better explained on the basis of secondary starvation? Is it possible to explain the picture on the assumption that it represents an infection due to a monilium and, if so, is one or several species involved? Or may various organisms or groups of organisms having the common quality of producing marked acid fermentative changes in the chyme bring about these symptoms? What role does diet play? May this possibly be a new member of the ever-increasing group of deficiency diseases? Is sprue very much more widely disseminated in temperate climates than has hitherto been supposed and may it play some role in certain of the vague chronic digestive disturbances so frequently met with in countries which lie in the southern portions of our temperate zones, for example, our southern states.

Whatever our answer be to these queries, we do feel that the study of our cases shows that in certain at least of the chronic cases of the disease (1) there is a practically complete absence of the pancreatic ferments, and (2) that while, obviously, all the well-recognized forms of treatment—dietetic, hygienic, etc.—should be rigorously carried out, nevertheless very great improvement and, in some cases, apparently clinical cure can be brought about by regular and constant administration of pancreatin.

EPINEPHRIN HYPERSENSITIVENESS AND ITS RELATION TO HYPERTHYROIDISM.*

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AND

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THERE are at the present time two procedures in extensive use in this country for the determination of functional hyperactivity of the thyroid gland. One of these, the measurement of the basal metabolism, rests on sound experimental and clinical observations, for there is abundant evidence that stimulation of the thyroid gland or administration of its active principle induces an increase in heat production. There can be little doubt that stimulation of metabolism is an important feature in hyperthyroidism and that the measurement of the metabolism is a valuable index of the degree of activity of the thyroid gland; but we are still in the dark as to how far other associated features combine with this and go to make up the clinical symptomatology of hyperthyroidism. The outstanding drawback to this method for the determination of thyroid activity is that even with the recently simplified technical procedures it requires specialized training and experience both for its application and for the proper interpretation of the information derived from it.

The second procedure consists of the injection of epinephrin and its diagnostic significance depends on the type of reaction which has been described as occurring in patients with hyperthyroidism, and which is supposed to be characteristic of this condition. The test is usually carried out by the method suggested by Goetsch, and 0.5 c.c. of a 1 to 1000 solution of epinephrin is administered.†

*.Read before the meeting of the Association of American Physicians, Atlantic City, N. J., May 5, 1920.

† The tests were actually carried out in the following manner, as described by Wearn and Sturgis (*Arch. Int. Med.*, 1919, xxiv, 247): "The patients remain at absolute rest in bed for a period of one hour. If there is restlessness or apprehension they should be reassured and every effort made to obtain mental as well as physical quiet. At the end of the rest period control readings of the blood-pressure, pulse- and respiratory-rates are made at five-minute intervals. Also at this time a note is made as to the presence of nervousness, precordial pain, dizziness, palpitation or any other symptoms which may be significant. Likewise the objective condition of the patient is observed, and it is recorded if any of the following signs are present: tremor of the hands, sweating, coldness of the hands, throbbing of the neck, epigastrium or over the precordium and pallor or flushing. At the end of an hour's rest in bed the patient is usually quiet and has few complaints; the blood-pressure and heart-rate are normal or there may be a slight tachycardia (in sharp contrast to the patient with exophthalmic goiter in whom a more marked tachycardia persists even when at rest in bed). Likewise after the rest period there is little to record from an objective or subjective standpoint. If this condition

The "positive" reaction which has been assumed to indicate hyperthyroidism consists of the production of a rise of systolic blood-pressure of at least 10 mm. of mercury or a rise in pulse-rate of at least 10 beats per minute, together with an increase of such signs and symptoms as tremor, sweating, vascular pulsation, nervousness and palpitation. The test is so easy to apply and apparently so simple to interpret that it has been widely adopted as a diagnostic measure, and the "positive" reaction is frequently considered as an indication even for surgical interference. On account of this tendency to regard the test as highly specific in its significance, it has seemed to be of importance to study in more detail the nature of the reaction to epinephrin and to determine the conditions under which the "positive" reaction, which may be assumed to indicate epinephrin hypersensitiveness, appears. Such studies have been carried on at U. S. Army General Hospital No. 9, Lakewood, N. J., and at the Peter Bent Brigham Hospital, Boston. The present communication is a brief summary of the results.

As far as is known the difference between "positive" and "negative" reactions to epinephrin is a quantitative one, and what clinical significance the test possesses depends on the selection of a proper differentiating dose. Even so small an amount as that used (0.5 c.c. of a 1 to 1000 solution) probably produces some effect in everyone. In subjects reacting wholly "negatively" it has been found that the basal metabolism is temporarily raised from 5 to 15 per cent., while in those reacting "positively" the increase is from 15 to 30 per cent.² No such effect is observed, even in nervous subjects, from the prick of a needle or from the injection of salt solution. Under given circumstances the effect of the drug seems to remain fairly constant in a given individual.

A fundamental part of the investigation obviously consists of approaching the normal has not been attained then the control readings should continue further, for with nervousness, tremor, sweating, tachycardia or possibly other prominent signs already present it would be difficult to judge the effect of the epinephrin. In a few patients the control readings of blood-pressure and pulse remained at a level slightly above the normal, but the injection of epinephrin was carried out after they became constant. In a number of patients venepuncture was done at the end of the rest period for blood-sugar determinations, but when this or any other disturbing factor is introduced it is necessary that subsequent control readings be made, and these should agree with the preliminary readings before the test can proceed. After satisfactory control readings have been made, 0.5 c.c. of a 1 to 1000 solution of epinephrin, freshly prepared, is injected deep into the deltoid muscle. In all of these tests the solution was made by adding one $\frac{1}{200}$ grain of Parke, Davis & Co. adrenalin brand of epinephrin tablet to 1 c.c. of water, thereby making a 1 to 1000 solution. After the injection four or five readings are made of the blood-pressure, pulse- and respiratory-rates at two or three-minute intervals, and also at these times any change in the objective or subjective condition of the patient is noted. After the first few observations readings are continued at five-minute intervals until one hour after the injection, when ten-minute readings are made for a period of one-half hour, thus making the observation period one and a half hours from the time of the injection. From our experience at Lakewood it would seem that the time of observation could safely be cut to one hour, as we have failed to observe anything of importance after that length of time."

the "control" observations carried out on normal individuals. These were begun in the army, and it was soon found that the problem was complicated by the fact that our standards of normality were not clearly defined. A number of patients in the hospital for minor surgical ailments turned out to be hypersensitive to epinephrin. Analysis of their past histories and of their characters suggested that while they were normal men, judged by the usual standards, they were not the types from which good soldiers are made. From the point of view of the army the "normal control" must be the soldier who can withstand the strain of hard training. A group of 26 men from an organization which had undergone training for fourteen months and was on its way overseas were therefore studied and none of these were found to give "positive" reactions to epinephrin. These were, of course, selected normals, for they were men of unusual physical endurance and nervous stability. A second group of normal men tested consisted of 28 Harvard medical students, and among these 4, or 14 per cent., gave perfectly definite "positive" reactions. Four other men showed transient rises of pulse-rate of over ten beats per minute, or of a systolic blood-pressure of more than 10 mm., or both. But as these were usually noticed only on one observation and not accompanied by the characteristic symptoms they were not regarded as giving "positive" reactions. In many other "negative" cases slight increase in blood-pressure and pulse-rate were noted. In addition to this there is a third group which may also be properly considered among the normals. These were patients at General Hospital No. 9 on whom the diagnosis of "effort syndrome" was made—men who, for the most part, would pass in civil life as within the bounds of normality but who developed symptoms, usually of a psychoneurotic nature, under the nervous and physical strain of army life. The exact nature of this condition is still uncertain, but there is very general agreement that hyperthyroidism plays no part in it. The clinical picture is not similar to that of hyperthyroidism; the subjects improve under therapeutic measures that make patients with hyperthyroidism worse, and the basal metabolism is normal. If so common a condition as "effort syndrome" represented even a mild or incipient type of hyperthyroidism it is almost inconceivable that definite cases should have been so rare in the army. Among 143 cases of "effort syndrome," 69, or 48 per cent., reacted "positively" to the epinephrin test. These results are not unlike those obtained by Boas,³ who reports that 28 per cent. of 21 cases of "effort syndrome" gave "positive" reactions. In association with this type of subject one may also consider the observations made on a small number of definite psychoneurotics—individuals who cannot be classed as wholly normal because the symptoms arising in the course of a normal life induced them to seek medical advice, but persons, on the other hand, in whom no evidence of organic disease,

either of the thyroid gland or of any other organ, could be found. Among 7 such subjects all were found to give "positive" reactions to epinephrin.

Summarizing the observations made on the various groups of subjects without evidence of organic disease, one finds that hyper-

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	HANDS	MISCELLANEOUS
9.00	—	—	—	—	COLD	RESTING QUIETLY
9.05	—	—	—	—	"	" "
9.09	—	—	—	—	"	" "
9.15	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY					
9.18	V. SL.	—	—	—	COLD	RESTING QUIETLY
9.21	—	—	—	—	"	" "
9.24	—	—	—	—	"	" "
9.27	—	—	—	—	"	" "
9.30	—	—	—	—	"	" "
9.35	—	—	—	—	"	" "
9.40	—	—	—	—	"	" "
9.45	—	—	—	—	"	" "
9.50	—	—	—	—	"	" "
9.55	—	—	—	—	"	" "
10.00	—	—	—	—	"	" "
10.05	V. SL.	—	—	—	"	" "
10.10	+	—	—	—	"	" "
10.15	+	—	—	—	"	" "
10.20	+	—	—	—	"	" "
10.25	+	—	—	—	"	" "
10.30	+	—	—	—	"	" "

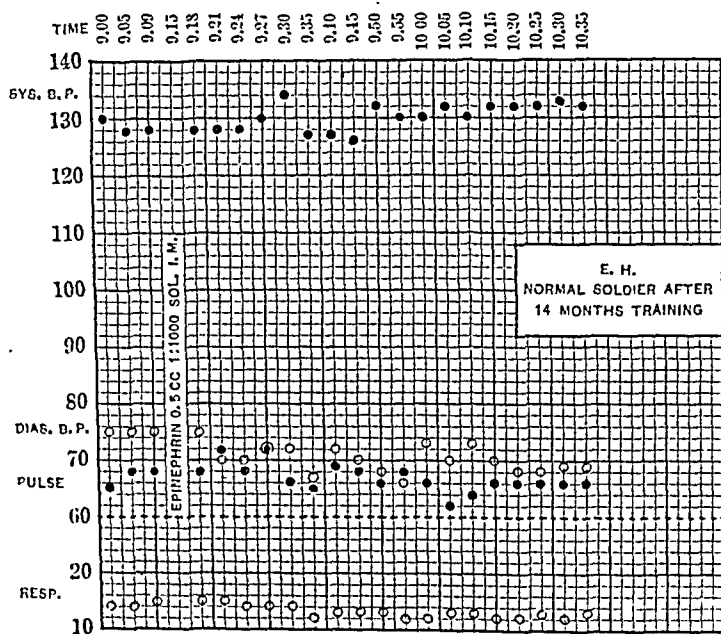


CHART I

sensitiveness to epinephrin is certainly not characteristic of the hardened soldier, that it occurs in about 14 per cent. of average young men, such as medical students, that it is present in nearly 50 per cent. of the type of young men who broke down under military training with the picture of "effort syndrome" and that it is still more common among definite psychoneurotics. It is difficult not

to see some relation between epinephrin hypersensitiveness and what one may call a "nervous constitution." On account of what is generally accepted as being known about the physiologic action of epinephrin, one is tempted to regard the test as indicating a hypersensitiveness of the sympathetic nervous system. It is frequently possible to select, on the basis of clinical study, the subjects who

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	MISCELLANEOUS
9.30	+	+	+	-	QUIET - EASILY DISTURBED BY VISITORS
9.50	+	+	+	-	"
9.55	+	+	+	-	"
10.00	+	+	+	-	"
10.08	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY				
10.10	++	++	+	+	SLIGHT RESTLESSNESS
10.13	++	++	+	+	RESTLESS
10.15	++	++	+	+	SHORT OF BREATH - PALPITATION
10.20	+++	+++	++	+	TWITCHING OF ARM AND CHEST MUSCLES
10.25	+++	+++	++	+	RESTLESS - NERVOUS - TWITCHING
10.30	+++	+++	+	+	DEFINITE REACTION
10.40	+++	+++	+	+	QUIETER - STILL VERY RESTLESS
10.45	+++	+++	+	+	TWITCHING LESS
10.50	++	++	+	+	QUIETER
10.55	++	++	+	+	"
11.00	++	++	+	+	"
11.10	++	+	+	+	QUIET
11.20	++	+	+	+	"

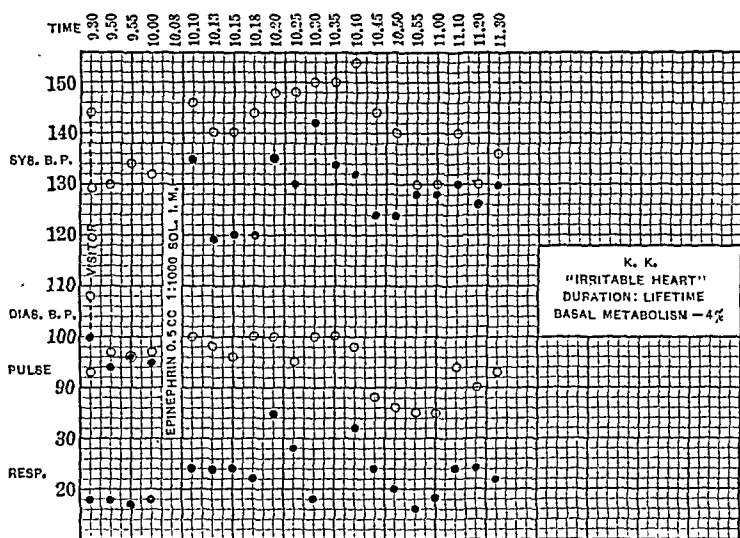


CHART II

will react to epinephrin, but this is by no means always the case. Even after considerable experience with the test one is liable to fall into error. There are many highly "nervous" or "neurotic" people who do not react "positively," and there are occasional persons who have no apparent neurotic tendencies who react violently to the drug.

The epinephrin test has also been used on various other types of

hospital case. Among 17 patients with organic heart disease, 3, or 17 per cent., gave "positive" reactions. This corresponds closely with the 14 per cent. of "positive" reactions found in the group of medical students, and it is possible that the figure represents approximately the average incidence of the reaction among normal persons. Incidental observations have also been made on cases of syphilis, chorea, asthma, acromegaly, epilepsy, diabetes, dementia præcox and hyperthyroidism, and one or more "positive" results have been obtained in each condition. In a series of 21 patients who were convalescent from acute infections, 12, or 57 per cent., gave "positive" reactions—a figure in close agreement with results obtained by F. M. Smith,⁴ who found that 50 per cent. of 50 cases following influenzal pneumonia reacted "positively." Nicholson and Goetsch⁵ report 19 "positive" reactions among 40 cases of questionable or definite tuberculosis, a percentage incidence of 47. One case observed at General Hospital No. 9 seems particularly worth noting. A boy with an organic heart lesion, but otherwise normal, gave a "negative" test. A few days later he had an attack of acute tonsillitis which was followed by a tonsillectomy. A repetition of the test, after convalescence from the operation, gave a "positive" result. This evidence certainly suggests that infections may induce a hypersensitiveness of the sympathetic nervous system, and there are, of course, various clinical symptoms which are in harmony with such a conception. To assume, however, that there is necessarily an associated hyperacidity of the thyroid gland seems quite unwarranted, if only for the reason that many of these post-infectious cases improve with graduated exercises, a type of treatment wholly unsuited to patients with hyperthyroidism. It is true that in certain cases with hyperthyroidism the condition has apparently manifested itself after some acute infectious disease, but the reverse is still more striking, for the development of outspoken hyperthyroidism after acute infections is without question more rare than it would be if there were stimulation of the gland in nearly one-half of the cases of acute infectious disease.

Case.	Disease.	Positive.	Negative.	Doubtful.
2	Pneumonia	2	0	0
3	Diphtheria	2	1	0
9	Acute rheumatic fever	4	4	1
1	Acute tonsillitis (tonsillectomy)	1	0	0
6	Scattered	3	3	0

Special attention has been paid to the epinephrin test in hyperthyroidism. The diagnosis in the cases reported on was based on the classic signs and symptoms and the history, together with the determination of the basal metabolism. Twenty-one cases have been studied, and in 15, or 71 per cent., "positive" reactions were obtained; 6 unquestionable cases, 4 in early stages and 2 in later stages, with basal metabolism ranging between 21 and 35 per cent.

above normal, gave "negative" epinephrin reactions. No relation was noted between the intensity of the reaction to epinephrin and the apparent severity of the case. One patient, with a basal metabolism 61 per cent. above normal, was considered to be extremely toxic but gave a comparatively slight reaction, while a mild case, with a basal metabolism 26 per cent. above normal, gave a very severe reaction. Nine patients were tested on whom thyroidec-

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	HANDS	MISCELLANEOUS
10.15	++	++	++	+	COOL	ONLY FAIRLY QUIET—MOVES ARMS AND HEAD
10.25	++	++	++	+	"	" " " FEW MOVES
10.35	++	++	++	+	"	" " " "
10.40	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY					
10.41	+++	++	++	PALE	COOL	NO CHANGE
10.41	++	++	++	PALLOR GONE	"	" "
10.48	++	++	++	+	"	" "
10.57	++	++	++	+	"	THINKS HER HEART IS BEATING FASTER
11.02	++	++	++	+	"	NOTICES NOTHING ELSE
11.07	++	++	++	+	"	FAIRLY QUIET
11.14	++	++	++	+	"	" "
11.22	++	++	++	+	"	" "
11.28	++	++	++	+	"	" "
11.38	++	++	++	+	"	" " NO SIGN OF REACTION
11.41	++	++	++	+	"	" "
11.52	++	++	++	+	"	" "
12.02	++	++	++	+	"	" "
12.08	++	++	++	+	"	" "

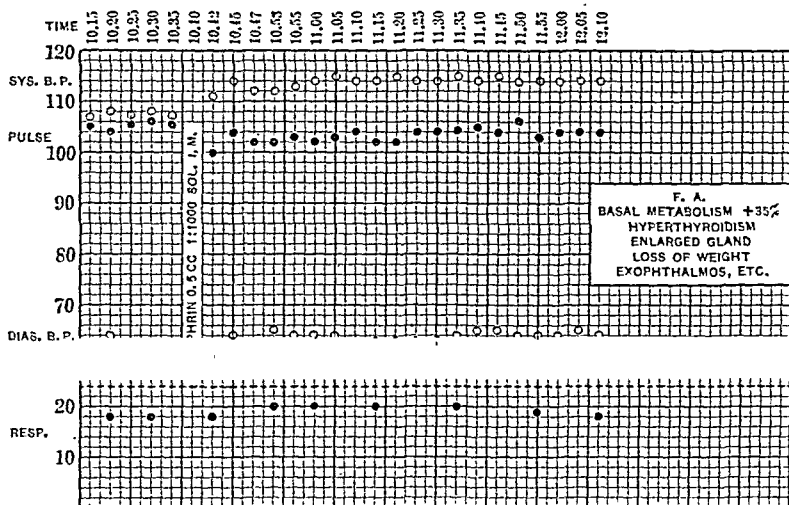


CHART III.

tomies had been done two or three years previously and who had been living normal lives without symptoms for a year or more. Five of them gave "negative" reactions, while 4, in whom the basal metabolism was -18 per cent., -15 per cent., -1 per cent. and +12 per cent., gave "positive" reactions.

The general conclusions which it seems justifiable to draw from our observations are as follows:

1. Different individuals, both sick and well, react with different degrees of intensity to the injection of epinephrin. By means of selected dosage of the drug and carefully chosen criteria for the response, one can differentiate, somewhat artificially, between the slight reactions which are called "negative" and the more violent

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	MISCELLANEOUS
3.15	++	++	+	++	VERY RESTLESS - MOVING CONSTANTLY
3.20	++	++	+	++	" " " "
3.22	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY				
3.25	++	+	+	6L. PALOR	RESTLESS AND MOVING
3.30	++	+	++	++	RESTLESSNESS INCREASING
3.32	+++	++	+++	+++	NERVOUS, EXCITED, THROBBING
3.35	+++	+++	+++	+++	NERVOUSNESS INCREASING, APPREHENSIVE
3.40	+++	+++	+++	+++	MARKED REACTION
3.45	+++	+++	+++	+++	SOMEWHAT QUIETER
3.50	+++	+++	+++	+++	" "
4.00	+++	+++	+++	+++	" "
4.05	+++	++	++	++	NERVOUSNESS DECREASING
4.15	++	++	++	++	" "
4.25	++	++	++	++	" "
4.45	+++	+	++	++	" "
4.55	+++	+	++	++	STILL MORE RESTLESS THAN AT START

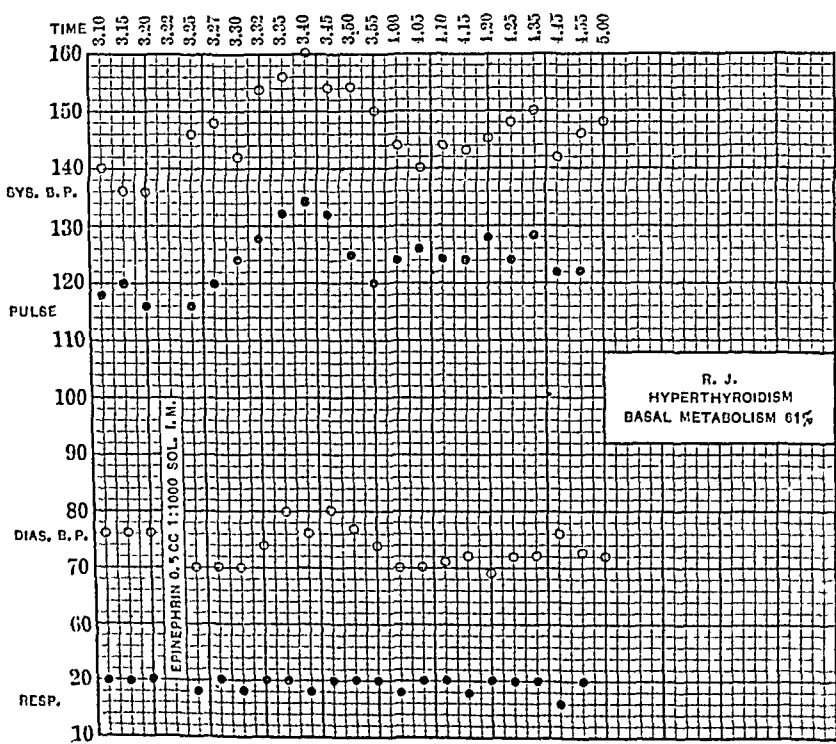


CHART IV

reactions which are called "positive." In certain instances "doubtful" or "questionable" reactions are obtained.

2. The fundamental nature of the reaction is unknown. It is associated with a rise in heat production which runs more or less parallel to the intensity of the reaction. On the basis of what is definitely understood with regard to the physiologic action of

epinephrin it seems probable that the phenomenon is due to a stimulation of the sympathetic nervous system. Theoretically a

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	HANDS	MISCELLANEOUS
9.50	+	+	-	+	WARM	QUIET
9.55	+	+	-	+	"	"
10.03	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY					
10.05	++	++	-	+	WARM	QUIET
10.07	+++	+++	+SL.	SL. PALLO	COOL	RESTLESS AND NERVOUS
10.10	+++	+++	+	+	"	MORE RESTLESS AND GENERALLY NERVOUS
10.15	+++	+++	+	+	"	REACTION INCREASING
10.20	++++	++++	+	+	"	"
10.25	++++	++++	++	+	WARMER	GENERALLY UNCOMFORTABLE
10.30	++++	++++	++	+	"	REACTION NOW MARKED PALPITATION, REST-
10.35	++++	++++	++	+	"	LESSNESS, VERY NERVOUS, FEELS QUEER
10.40	++++	++++	++	+	"	NUMEROUS EXTRA SYSTOLES
10.45	++++	++++	++	+	"	REACTION CONTINUES
10.50	++++	++++	++	+	"	"
10.55	++++	++++	++	+	"	"
11.00	++++	++++	++	+	WARM	
11.05	++++	++++	++	+	"	BEGINNING TO FEEL BETTER QUIETER
11.15	++++	++++	+	+	"	HEART ACTION REGULAR FEELS "FINE"
11.25	++++	++++	+	+	"	
11.35	++++	++++	+	+	"	NOW FEELS COMFORTABLE

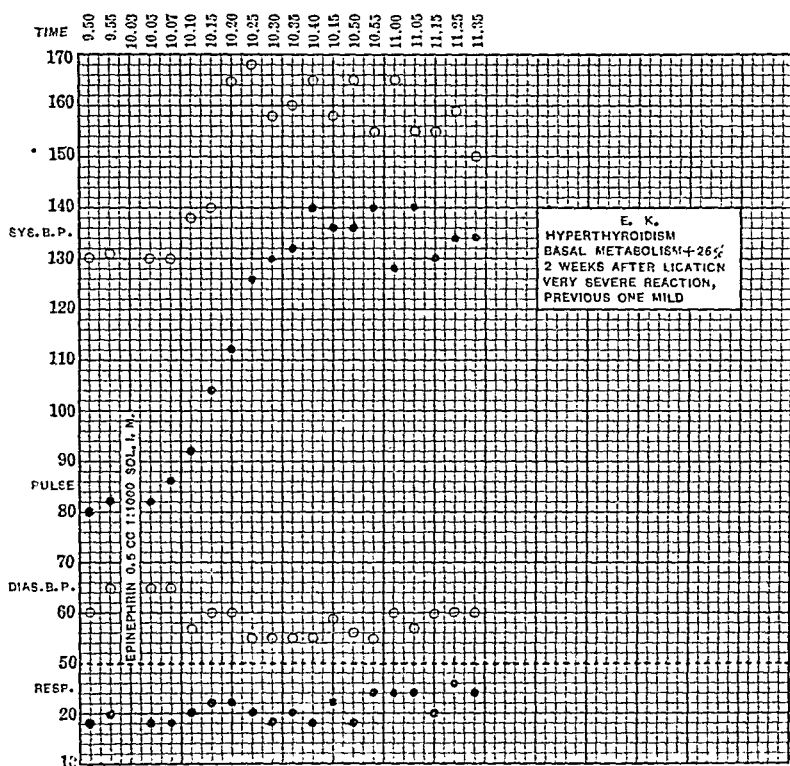


CHART V

"positive" reaction might indicate hyperactivity of the thyroid gland; of the adrenal glands or of the sympathetic nervous system. It might, on the other hand, depend on a lowered threshold of

response of the sympathetic nervous system. With the exception of hyperthyroidism little is known about these conditions in man, but they probably occur and there would seem to be no reason for assuming that a "positive" epinephrin reaction is constantly associated with hyperthyroidism. It is much more likely that different causes account for the reaction in different types of clinical cases.

3. Hypersensitiveness to epinephrin is found in many patients with the clinical picture of hyperthyroidism and with an increased basal metabolism, but it is not constant under these conditions.

4. Hypersensitiveness to epinephrin is also found in persons who have no indications of hyperthyroidism. Thus it was present in many psychoneurotics in about 50 per cent. of patients convalescent from acute infections, in nearly the same proportion of soldiers with "effort syndrome," in 14 per cent. of apparently normal young men and in patients with various unrelated diseases.

5. The "positive" reaction to epinephrin appears to occur most often in highly nervous individuals, but it is not constant in such persons. The clinical significance of the reaction is not clear, but at present it should certainly not be regarded as having any specific significance in the diagnosis of hyperthyroidism.

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THE USE OF DIET IN THE TREATMENT OF CHRONIC ARTHRITIS.

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IN a series of previous contributions the writer has published the results of laboratory and clinical studies upon chronic arthritis which reached their fullest development in the course of observations upon soldiers in the army.¹ The scale upon which these last observations were conducted was much larger than has heretofore been possible in this country under controlled conditions, and in addition to yielding side lights upon existing views, afforded further data and directed attention along new lines.

¹ Pemberton, Buckman, Foster, Robertson, Tompkins: Studies on Arthritis in the Army Based on Four Hundred Cases, Arch. Int. Med., March, 1920, xxv, 231-232; April, 1920, xxv, 335-404.

One of the chief methods of investigation employed arose from earlier observations upon the relation of a limited food intake to the incidence and perpetuation of the symptoms of chronic arthritis. In the course of this investigation, clinical experience in the application of dietary control to this disease was not a little amplified, and the matter was further placed upon a firmer foundation by a number of laboratory findings.

The writer's personal acquaintance with colleagues at scattered points, as well as correspondence and indirect information from others not personally known to him, has indicated that these methods are being utilized in the treatment of arthritis, and it seems important to direct attention to several considerations. The purpose of this article is therefore to make brief mention of the added experience gained in the application of diet to arthritis; to call attention to the greater justification for the use of these methods which laboratory observations have afforded; to point out the place which these methods occupy in relation to other forms of therapy in this disease; and, finally, to direct attention to the limitations in the application of these methods, to the precautions which must be observed and to the possible dangers from neglect of these precautions.

Without going into details which have been elsewhere fully published (*loc. cit.*) mention can here profitably be made, by way of preface, to several of the positive findings in the army studies above referred to. There were observed a very slight lag in the eliminations of salt and water in arthritics as compared to normals; a basal metabolism slightly lowered in 20 per cent. of the cases; a high blood creatin which tended to disappear as cases improved; a lowered sugar tolerance which was found to accompany arthritis more or less in proportion to its severity. Essentially normal data were obtained regarding the blood fats and cholesterol, the blood calcium and the blood urea and non-protein nitrogen. The statistical findings regarding etiology, distribution of involvement, etc., need not be referred to here.

The lowered sugar tolerance was determined by the administration of 100 grams of glucose by mouth and the subsequent estimation of the percentage concentration of glucose in the circulating blood. In 200 observations on 60 arthritics this lowered sugar tolerance was found to grow less or disappear as convalescence proceeded, whatever the method of therapy, but it returned to normal most abruptly after the removal of causative foci of infection. A lowered sugar tolerance is not specific for arthritis and should be interpreted only as reflecting part of the underlying pathology of this disease which, on a number of counts that cannot here be detailed, apparently consists in an interference with the respiratory functions of the circulating blood. These do not, however, express them-

selves conspicuously in terms of the end-metabolism as shown by basal metabolism studies.

As already mentioned the application of the principle of a reduced diet to arthritis received amplification in the above studies, particularly as to its use in combination with other forms of treatment and as to the vigor with which it could be applied. An attempt will therefore be made to outline the manner in which the dietetic handling of a case can be most simply carried out and then to indicate the limitations and contra-indications to this therapy.

A preponderating number of chronic arthritics, if placed upon a sharply reduced intake of food or on a starvation basis, will show within a period of one to four days a betterment in their subjective feelings, lessened tension of the soft tissue, and an added freedom of movement. The improvement may follow upon intercurrent surgical operations of many kinds and examples of such improvement, together with criteria as to the early evidences of clinical betterment, are detailed in the references already given. The improvement under sharp dietary restrictions may and generally will be seen, even in the presence of causative foci of infection, because the principle under which it acts is that of catering to a weakened function, probably an oxidative function, dislocated in most cases by some inflammatory process usually in the form of focal infection. Following upon a chronic focus of infection, however, there may be a more or less permanent dislocation of normal physiology, as illustrated by the lowered sugar tolerance, such that removal of the focus is not sufficient to restore it, and it is particularly for this reason that disappointing results so frequently follow the removal of definite infectious foci. Notwithstanding the possibility, however, of demonstrating the benefits from a reduced caloric intake even in the presence of focal infection, therapy based upon this should never be attempted in the presence of such removable infection. This is one of the precautions which the writer desires to emphasize in the strongest possible manner. It would be obviously unsound to attempt treatment by adjusting conditions to the limitations of a weakened function if the cause of that weakened function can be removed. There are contra-indications to the removal of foci which make such action justifiable occasionally but the chief field of use for dietetic therapy in active arthritis is that in which focal infection definitely cannot be demonstrated, or, better, has been definitely removed without further clinical improvement.

In cases of chronic arthritis suitable for dietetic therapy, treatment must be carried at least to the point where the individual is spared the necessity of metabolizing as much food as he had been previously ingesting. There are unfortunately few criteria, except subsequent clinical improvement, of the degree to which the diet must be reduced, and it therefore follows that it is generally useful

to know what the accustomed caloric intake of a given case has been under the average conditions of his invalidism. This is by no means always essential, but it becomes so more or less in proportion to the severity of a case and the prospective difficulty of treating it. If the patient be ingesting customarily a fairly large amount of food, say 3200 calories, it is obvious that this quota can be significantly reduced to, say, 2200 calories without great detriment to his nutritive needs, at the same time sparing him about 1000 calories. If, on the other hand, the accustomed food intake of an arthritic be 2000 calories or less, as is frequently the case in later stages of the disease, the administration of a diet of 2300 calories would not only fail to achieve its purpose but might tend to aggravate existing conditions. The writer has therefore found it useful to determine over a period of a week or ten days, under conditions approximating the average life of an individual the accustomed food intake in terms of calories. This can be done within a relatively small margin of error in any modern hospital where the services of a trained dietitian are available. It is also useful occasionally, in chronic cases, to know the percentage distribution of calories from protein, fat and carbohydrate, because of the indications that of all these foods carbohydrate is the chief offender by virtue of its quick combustion and the large role which it plays in average dietaries. Such an estimation, however, is not essential and the total calories are of greater importance. It has been determined over a considerable series of arthritics that relatively early cases of arthritis in good nutrition, accustomed to a food intake of 2800 to 3000 calories or more, may do very well from the start and shortly recover entirely following a reduction of their caloric intake to about 2000 calories. It is often possible in these cases to increase this total by two or three hundred calories, preferably from fat, a few weeks after convalescence is well established. Under these circumstances dietetic therapy, by catering to a mildly weakened function, has one of its happiest results. In more extreme types problems of much difficulty may arise, although the principle of treatment is not altered. If, for example, as above mentioned, the accustomed daily caloric quota has been for a year or more 1800 or 1900 calories, any attempt to spare the metabolic functions by cutting this down may be at the further expense of nutrition as a whole and can be carried out only with the greatest caution. The experience of the profession with diabetes has shown the degree to which low diets can be often successfully borne, but in view of the fact that arthritis is not a fatal disease *per se* the justification for applying them to it must be very clear.

When it becomes necessary to institute a food intake below 1800 calories it is well to begin at the highest level from which, *a priori*, any results can be expected, say 1500 calories. If results are not forthcoming at this level it may be necessary to reduce the total for a short time to 1200 or 1300 calories, in anticipation of

which an intermediary period of "feeding-up" may be advantageous. At about 1500 calories the arthritic confined to a wheeled chair or to bed may easily maintain a fair nutritive balance but below that point conditions of undernutrition are established and should not be entered upon without considerable familiarity with this field and the possible dangers entailed. Short periods of undernutrition at these levels are, of course, not necessarily fraught with danger, but unless constituting part of a specific program are likely to do more harm than good. The early clinical betterment which is inaugurated, but cannot necessarily be maintained, leads to false encouragement and unnecessary depletion. The general nutrition of a subject is an important factor in determining the degree to which treatment can be pushed and the individual, not the arthritis, must often determine the vigor of treatment. It is of small benefit to improve the arthritis at the serious expense of the patient's health as a whole.

In addition to treatment by a reduced dietary, however, it is sometimes possible by an absolute fast to demonstrate quite dramatically a marked change in nearly all the manifestations of a severe arthritis. The adoption of such procedures, however, is not to be recommended for general use at the present time because of the critical undernutrition which results and because of the very disturbing if not dangerous complications which may arise. In the studies in the army, previously mentioned, is given a detailed account of a case treated along these lines with most gratifying end-results in so far as the active arthritic process was concerned (Case 22 of the above report). The soldier in question was again under observation almost a year later and was found to have maintained his freedom from active arthritis and to have gained greatly in strength and activity. It is, nevertheless, partly to direct attention to the untoward results which may follow such measures if carelessly applied and to urge the greatest caution in conducting them that the present article is contributed.

In addition to the precautions urged above must be mentioned again the limiting influence, in a given case, of such factors as anemia, undernutrition, intercurrent diseases of various kinds, functional nervousness and greatly lowered morale from invalidism. Coöperation, persistence and courage on the part of the patient are almost invariably required, and even in the most promising cases the physician may have to supply the *vis a tergo* in respect to each of these.

It is the misfortune of clinical medicine that the recognition of a new method of therapy is almost invariably followed by some unwise and extreme application of it. There is no such thing as a panacea or specific in our armamentarium, and, as a rule, injuries from abuse are necessary before wise utilization of any new therapy is possible. The present writer cannot hope entirely to escape this

result but can at least urge conservation and caution until the possibilities for good and evil have been more thoroughly worked out. This is of the greatest importance because the benefit to be derived in a definite percentage of arthritics from the method under discussion is now quite beyond dispute.

As a result of the studies above mentioned, and also of work now under way, the nature of arthritis can now apparently be definitely categorized, and indeed pretty clearly outlined.

Over a year ago the writer gave the reasons for his belief² that arthritis is due to interference with the processes of oxidation, possibly in the respiratory functions of the blood, and some outline of the manner in which this operates is given in a recent summary of some known and suggested facts related to arthritis, together with a hypothesis as to its nature.³

Space will not permit of discussing this question further at this point, but suffice it that the principle of action seems to apply to cases of all severity except that, in the more severe types, "catering" to a weakened function in the manner described may not alone suffice to restore altered physiology to normal. The situation is perhaps analogous to that presenting in cardiac decompensation, where the keynote of all treatment is rest. After a certain degree of decompensation is established, however, rest alone is not adequate and must be reinforced by such therapy as digitalis although the guiding principle must still be maintained.

By the same token, advanced arthritis should be treated with a clear understanding of the basis upon which therapy should be built, and one of the results arising from increased experience with this disease lies in appreciation of the fact that combinations of different kinds of treatment will often achieve results where dependence upon one measure alone will fail. Thus if the arthritic be spared unnecessary metabolic burdens he will often respond more readily to such a measure as hydrotherapy which by itself is too frequently unavailing. From the evidence now at our command it seems more than probable that reduced diet, hydrotherapy, the iodides, arsenic and certain other agents really act all in the same direction, differing chiefly in the manner in which they accomplish their end-result. Caution must again be urged here, however, against the depletion which may follow several coincident lines of attack unless critically carried out.

From what has been said it is obvious that no rule can be advanced for determining the level of the appropriate diet in any given case, but the nearest approach to such a help is based upon the recognized approximate requirement of 30 calories per kgm. of body weight under resting conditions. If reasonable precautions be observed this is probably a safe nutritive level under most circumstances, and

² Address before the New York Academy of Medicine, November 16, 1919.

³ Jour. Am. Med. Assn., December 25, 1920, No. 26, vol. lxxv, p. 1759.

if the total calories so determined be contrasted with the caloric level under the previous conditions of the individual's life the observer will often be surprised at the sharp reduction evidenced. It must not be supposed, however, that this will necessarily achieve the desired result in all cases. It is probably fair to say, however, that this level should be established in many refractory cases as a foundation for other forms of therapy that might otherwise be inoperative.

The details of the composition of diets constructed along the above lines have been already fully published and space will not permit of their repetition here.⁴ Attention should be called, however, to the principle of giving the individual as much satisfaction as possible at his meals by serving bulky substances of small nutritive worth. It is thus possible to provide what appears to be a fairly generous meal, although the amount of actually nutritious substances, such as eggs, bread, butter, milk, etc., which form the source of the calories in the diet may be very limited.

It may be useful at this point by way of illustration to cite two instances of improvement through the combination of several measures on the basis of a restricted diet.

Miss B., aged twenty-seven years, had for several years suffered from a violent widespread arthritis of the proliferative type characterized by atrophy of the joint structures and great swelling of the soft tissue surrounding them, most evidenced in the hands. She had been through nearly every conceivable form of examination and treatment, including removal, on principle, of her tonsils, but without benefit. The only thing which had proved of any value was thyroid extract and this induced such a serious disturbance on its own account that it was discontinued. She then relapsed. The accustomed food intake of this patient under uninfluenced conditions average about 2415 calories. She was then placed upon a caloric level of 1558 calories for three weeks, with definite evidences of improvement, in the form of relaxation in the soft tissues of the phalanges of the hands and subjective *bien aise*. After several changes of diet following a gastro-intestinal upset it became clear that the above caloric intake should be further reduced, as conditions were apparently stationary. She was therefore placed upon 1358 calories to which was added a very cautious regimen of sweats every other day, and in a few days experienced distinct further benefit. It is hoped later to publish further details of this case together with certain laboratory observations.

Another instance of benefit following the application of orthodox measures after the removal of an unnecessary "metabolic load" is the following already published in the studies quoted.

⁴ AM. JOUR. MED. SC., May 1917, No. 5, vol. cliii, p. 678, The Metabolism and Treatment of Rheumatoid Arthritis. Fourth paper. Ralph Pemberton, M.D.

Stg. Hays, aged twenty-nine years, had suffered for two years from a progressive and ankylosing arthritis chiefly of hands and wrists. Two months after tonsillectomy and several months after removal of dental foci there was no improvement. A careful search could reveal no other focus of infection. Observation of this patient for eleven days showed him to be ingesting an average of 3000 calories per diem. He was then placed on a diet of 2051 calories and twelve days later there was unquestionably less tenderness and swelling, and probably greater freedom of movement than at any time during the two months of observation. This improvement was maintained for some weeks, when his condition became stationary after about 50 per cent. improvement. After some oscillations of diet he was again placed on the same regimen, to which were added hydrotherapy cautiously conducted, potassium iodide and cod-liver oil. Further improvement was again inaugurated, and about a month later he left the hospital, with no evidence of active arthritis anywhere.

Attention should be directed to the fact that in the early stages following the institution of a sharply reduced diet there may be a rapid loss of weight. Under these circumstances improvement of the arthritis may be very striking, due to the fact that catabolism is running ahead of anabolism. This condition can be compared to the hastened metabolism following such stimuli as radium and the roentgen ray. As the plane of basal metabolism falls, however, to a lower level and becomes adjusted there with equilibrium of weight, improvement may be much less obvious or may even cease entirely. At this time there may indeed be in severe cases or in those in which the appropriate level of diet has not yet been reached, an exacerbation at some point notwithstanding the recent improvement.

It is at this time the test of the applicability of a diet arrives and it then becomes necessary either to hasten metabolism further by means of several agents available to this end, hydrotherapy, arsenic or possibly potassium iodide, or else further to reduce the diet in the manner discussed. The principle of betterment under a reduced diet may be well illustrated under these circumstances, and yet the clinical application of it may fail unless these relations be appreciated.

In a few cases under the writer's care no beneficial influence from a reduced diet could be detected, much less carried to a clinical conclusion. The proportion of cases, however, which show no evidence of favorable operation of the principle of a reduced diet, even short of true clinical betterment, is small in the writer's experience; but there seem undoubtedly to be some such instances, and one should be prepared to meet them. It should also be remarked that even during improvement under properly adjusted dietary conditions there may be exacerbations at one or more points temporarily interrupting progress. If these be treated

symptomatically or even left alone and the main principle adhered to they will often subside, become less severe and frequent as time goes on and finally disappear.

Attention has been previously directed to the fact that when convalescence is thoroughly established an increased caloric intake is often possible sometimes to such a degree that the individual can resume his previous activities with even added efficiency.

It is impossible, without going to too great length, to particularize regarding factors and signs which should be observed in carrying a case of arthritis over the long road to recovery. Experience alone will yield them. The point has been reached, however, at which a further addition of exact data has placed the treatment of arthritis by low caloric feeding upon a basis more secure than existed previously, so that the principle of application can be appreciated even in the presence of departures from rule. It is hoped to publish further data in this connection in the not distant future.

THE PATHOLOGY OF BRONCHIAL ASTHMA.

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TWELVE years ago one of us (A. G. E.) discussed in this JOURNAL¹ the pathology of bronchial asthma as based on a study of 7 previously reported cases and 1 personally added. The conclusion reached at that time was that there is no constant or definite change in the bronchi of persons dying during an attack of this condition. Since that time 3 additional cases have been reported. The history of one of these was published in the *Transactions of the German Pathological Society* for 1909. The other 2 are the more recent ones of Brown² and Boughton.³ The first 2 are not accessible to us.

The case of Boughton was reported as one of death from anaphylaxis and followed the injection of one minim of horse serum as a desensitizing agent. The effect of the injection of that minute quantity of serum was a typical attack of bronchial asthma, with fatal termination, in forty-five minutes. The subject was an otherwise healthy man who for ten to twelve years had suffered attacks of asthma when in proximity to horses. Post mortem the lungs

¹ 1908, cxxxvi, 407.

² Asthma, St. Louis, 1917.

³ Jour. Am. Med. Assn., 1919, lxxiii, 1912.

showed emphysema. Microscopically there was a little mucus and a few desquamated epithelial cells in some of the bronchioles—not more than a slight catarrhal bronchitis if it can be called that. Boughton does not mention the sputum of this patient.

To these cases we can now add a twelfth, recently studied in Siriraj Hospital. Clinically it is of interest because of the family history of asthma in four generations. Furthermore, the duration of the disease, with attacks from childhood to the age of fifty-two years, would supposedly lead to permanent histologic changes in the bronchi if such ever occur in this affection.

History of Case. The patient was a Siamese man, aged fifty-two years, at one time an actor but chiefly engaged as a fishmonger at a seaside town. He did not smoke opium nor Indian hemp. His grandmother (father's side), father, an uncle and an aunt had asthma and the patient's third child is also suffering from the affection.

Patient since childhood had suffered from attacks of asthma, which at first were at long intervals but gradually became more frequent. Three months before admission to the hospital his feet and legs began to swell, this finally including the whole body. Coughing and shortness of breath were for a long time prominent symptoms, both gradually becoming more marked. On admission the man was edematous, ascitic, cyanosed and had respiratory dyspnea, with abdominal breathing and respirations, thirty-four to the minute. He had a troublesome cough, productive of white, tough sputum (this was not examined in the laboratory). Rales were present, especially over the bases. The precordial area was resonant and heart sounds weak. Treatment gave no relief; the patient gradually became worse and died on the eleventh day after admission, clinically from heart failure.

Postmortem Findings. The body was edematous. All the serous cavities, except the left pleura, which was obliterated by adhesions, contained a marked quantity of serum. The right auricle and ventricle were dilated and contained fluid blood under pressure. The wall of the right ventricle was 1 cm. thick. The left ventricle was moderately dilated; the muscle was red and firm. Valves and vessels were normal.

The left lung was collapsed to about one-half the usual size. The incised surfaces were dark bluish-red in color. Crepitation was much lessened but there was no actual consolidation. The bronchial mucosæ were intensely red. In the middle-sized and smaller bronchi was tenacious mucus, but not in great quantity.

The lower lobe of the right lung was like the left and the bronchi were similar. The upper and middle lobes were overdistended and at the apex were subpleural blebs. These lobes pitted on pressure, were pale and on incision dripped frothy serum. Crepitation was

lessened but there was no consolidation. The bronchial mucosa in these lobes was pale and the luminae contained no exudate.

The abdominal organs contained an excess of blood. Summary: Hypertrophy and dilatation of right ventricle; dilatation of right auricle and left ventricle; bilateral chronic adhesive pleuritis; partial atelectasis of left lung and lower lobe of right; vesicular and interstitial emphysema of upper and middle lobes of right lung; acute bronchitis of left lung and lower lobe of right; congestion of spleen, kidneys, stomach and liver; anasarca; multiple serous effusions.

Spreads of the exudate in the bronchi are of leukocytes and many columnar epithelial cells. In the cellular mass is much mucus and a number of very typical Curschmann's spirals. Charcot-Leyden crystals are not present and staining reveals only an occasional eosinophile.

Microscopically the partly collapsed portions of the lungs contain considerable black pigment, with at points fibrous tissue increase around it. Most of the epithelial lining of the bronchioles is desquamated and its place is occupied by leukocytes, nearly all mononuclear, which also partly fill the lumina. The vessels in the walls are intensely hyperemic and the tissues are densely infiltrated by mononuclear cells. In the middle-sized bronchi epithelial desquamation varies in degree, but in general is less than in the smaller ones. In the lumina are many mononuclear leukocytes and some red blood cells. In some of these larger tubes is a small quantity of mucus but no spirals. In none of the bronchi are crystals or eosinophiles. There is no evidence of fibrous tissue thickening of the bronchial walls nor does the muscularis mucosa appear abnormal. The larger bloodvessels are somewhat sclerotic. The bronchi in the expanded portions of the right lung have much less marked changes, indicating that the compression atelectasis of the other parts had increased the catarrhal changes.

The histology of the bronchi may therefore be summarized as that of an acute catarrhal bronchitis. We have in this case then to deal with a man who had had increasingly frequent attacks of asthma since childhood, but with no greater changes in the walls of his bronchi than might develop in a few days during an acute inflammation without asthma. As to the bronchial content, spirals are, of course, not commonly found in catarrhal exudates, but they have been encountered, according to Kaufmann, in cases of lobar and bronchopneumonia, fibrinous bronchitis, pulmonary edema and behind bronchial stenosis due either to enlarged pigmented glands or peribronchial malignant tumors. They are therefore not specific either in origin or in significance when found in the sputum, although, of course, much more common in cases of bronchial asthma. Nothing in the structure of the bronchi explain their formation in any case.

In conclusion, these additional cases still further emphasize the conclusions of the former paper, namely, that the histology of the bronchi does not explain the course of bronchial asthma. The length of time a person suffers from the disease and the number of attacks he has are apparently without effect upon the bronchi. The theory of spasm of the bronchial muscles, while not thus proved, is by each case increasingly favored.

INFLUENZA.*

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IN considering the subject of "influenza," it is important to have clearly in mind to just what disease one is referring. The disease which will be discussed in this communication is the one which appeared as a pandemic in the autumn of 1918 throughout the United States and has appeared subsequently, with pretty general distribution, during the winters of 1918-19 and 1919-20. Just what relation this disease, which appeared in pandemic form, bears to the conditions ordinarily spoken of as influenza, grippe, fever of unknown cause, acute respiratory infection, etc., is not clear. It is possible that the pandemic disease was simply one of these in which the virus had become temporarily intensified, but it seems more likely that it was an independent disease.

In order to have a clear conception of this condition called influenza, it is exceedingly important to separate the disease itself from the subsequent complications. This is rendered additionally difficult because the etiology of the pandemic disease is not settled. If the influenza bacillus eventually turns out to be the cause of this pandemic disease, many of the lesions which are now looked upon as complications will have to be considered as part of the disease.

The etiology of this pandemic disease has been the subject of considerable discussion. This has narrowed itself down practically to the question of whether the influenza bacillus described by Pfeiffer following the epidemic in 1889-90 or some other unknown organism was the causative agent. At one time it was suggested that this pandemic disease might be some form of the plague, but it is now felt by most authorities that such was not the case. Folley¹ aroused considerable interest in regard to the etiology of this disease by reporting the presence of a coccobacillus similar to the plague organism in the blood serum in many of these cases, but his findings have not been confirmed by other observers.

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In favor of the view that the influenza bacillus was the cause of the pandemic disease is the frequency with which it has been recovered from the secretions of the nose and throat. Opie² and others and Roos,³ among others, have shown that this organism was present frequently in the secretions from this part of the body. Wolbach⁴ in his autopsy studies found the sinuses leading off from the upper respiratory tract frequently infected and in many cases recovered a pure culture of the influenza bacillus. Roos by injecting the influenza bacillus produced lesions in the bronchial tract and also a leukopenia in rabbits. It is a well-established fact that during the early stages of this pandemic disease the leukocytes in the blood stream were usually diminished. Huntoon and Hannum⁵ have isolated an endotoxin from cultures of the influenza bacillus which has produced a specific lesion in the lungs of mice. They also found no serologic characteristics which would interfere with the claim that the influenza bacillus was the etiologic factor in this pandemic disease. Ferry and Houghton⁶ found congestion throughout the various organs of guinea-pigs and marked prostration in rabbits following injection with the influenza bacillus, both of which symptoms occurred in man during this disease. Blake and Cecil⁷ have produced in monkeys by inoculation with the influenza bacillus a disease which they consider similar to the pandemic disease in the human.

Against the opinion that the influenza bacillus was the etiologic factor in the cause of this pandemic disease may also be arrayed a considerable amount of experimental evidence. In many instances the influenza bacillus has not been isolated from the upper respiratory tract even after careful bacteriologic studies and also the influenza bacillus has not been recovered in the blood cultures by various observers including Matz.⁸ Rosenau and Keegan,⁹ as well as Goldberger and Lake,¹⁰ endeavored to produce this disease in human subjects by various experimental procedures with the influenza bacillus, and in all cases were unable to do so. Bloomfield¹¹ has placed different strains of the influenza bacillus upon normal mucous membranes of the upper respiratory tract but has not produced any disease by this experimental procedure. Valentine and Cooper¹² feel that this pandemic must have been produced by one specific organism, and consider the fact that various strains of the influenza bacillus were found among the different cultures is an argument against the pandemic having been due to the influenza bacillus. Tunnicliffe¹³ found that the opsonic curve toward the influenza bacillus was not influenced during the course of this disease and therefore considers that this organism is not the etiologic factor. Goodpasture and Burnett¹⁴ have reported the presence of lesions in the lungs which they consider typical of the cause of this pandemic disease in certain cases in which the cultures from these lungs have remained sterile. As the influenza bacillus was frequently recovered from the lungs in

their cases its absence in these cases with typical lesions makes them feel that it was simply one of the secondary invading organisms. Neal¹⁵ brings out the fact that during the pandemic there was no more influenzal meningitis than one normally meets, and he feels that one would expect a large increase in this type of meningitis if the disease were due to the influenza bacillus.

At the present time it is justifiable for difference of opinion to exist in regard to the etiology of this pandemic disease. For convincing evidence has not been presented either for or against the influenza bacillus as the etiologic factor. Park¹⁶ states that the organism which produced this disease is as yet unknown and that the influenza bacillus was a frequent secondary invader. It certainly is fair to say that no other organism has been reported which may be considered as the producer of this disease.

In what manner this pandemic disease was spread is not established. It was assumed that direct extension from one individual to another by means of droplets from the respiratory tract containing the virus which contaminated the air, eating utensils, clothing, etc., was the method of transmission. Experimental work by Rosenau and Keegan⁹ and Goldberger and Lake¹⁰ have thrown considerable doubt upon this method of transmission because both sets of experimenters working independently were unable to infect human volunteers with secretions from the upper respiratory tract of patients ill with the disease. Leake¹⁷ has continued experimental work with human volunteers along the same lines as these other investigators, and although he has failed in the great majority of cases to produce this disease by introducing human secretions from the respiratory tract of acutely ill patients into the upper respiratory tract of volunteers, he has in rare instances produced a disease similar to the one met with in the pandemic. The very rapid spread of this disease in a community was similar to that seen in water or milk-borne epidemics rather than the epidemics dependent upon direct extension from one person to another. Lynch and Cumming¹⁸ have shown from a study of statistics that the washing of eating utensils by means which do not sterilize them and the wash water was a serious factor in the spread of this disease. Winslow and Rogers¹⁹ feel that it was spread by human contact or the contamination of food, etc., because in Connecticut it was possible to keep certain communities free from the disease by strict quarantine.

In considering the pathology of this pandemic disease it is exceedingly important to keep separate the lesions produced by the disease itself from those dependent upon the secondary invading organisms. The respiratory tract presented the most striking lesions. Throughout the upper respiratory tract and bronchi the mucous membrane was markedly congested and hemorrhage into it was not infrequent. In the smaller bronchioles and the adjoining alveoli there was a degeneration and necrosis of the cells forming the walls resulting

in a peculiar hyalin formation. This has been reported independently by MacCallum,²⁰ Wolbach⁴ and Goodpasture and Burnett.¹⁴ At first there was very little fibrin deposited, but this sometimes appeared later. Into the air spaces from the injured walls hemorrhage often occurred. It is possible that this lesion progressed at times into a bronchopneumonia without any secondary invading organisms, but probably not. The bronchioles became dilated, probably due to the necrosis of their walls. This in some cases led to permanent bronchiectasis, but it also is not certain that this occurred unless some complicating organism was present. Actual ulceration of the bronchi has been reported by Lucke, Wight and Kime.²¹ Escape of air into the interlobular tissue of the lungs with extension into the mediastinum and subcutaneous tissues sometimes occurred. Congestion of and hemorrhage into the bronchial lymph nodes was found. Hemorrhagic lesions in the adrenal gland similar to those found in other acute infections has been reported, and atrophy of the cells of the adrenals has been noted by Cowie and Beavan.²² Degeneration of the parenchymal cells of the testes with little cellular reaction was noted by Wolbach.⁴ Several observers have mentioned a hyalin degeneration of the recti muscles and acute arteritis has been noted in these and other muscles.

Although the lesions dependent upon the pandemic disease itself were somewhat limited except for the respiratory tract, the lesions resulting from the invasion by complicating organisms were most varied. Unfortunately many authors in describing the pathology of so-called influenza include the lesions produced by secondary invading organisms, which results in some confusion. The character of the lesions met with in the complications varied with the invading organism and the location of the lesion. The organisms which have been reported as complicating the pandemic disease are the influenza bacillus; all four types of the pneumococcus; the *Streptococcus hemolyticus*, the *Streptococcus viridans*; *Staphylococcus aureus*; *Micrococcus catarrhalis*; and the Friedländer's bacillus. If the influenza bacillus eventually is found to be the cause of this disease the lesions produced by it, of course, will no longer be considered complications.

Of the various complications the lesions produced in the lungs have been the most interesting and have received the most attention. Of these pulmonary lesions bronchopneumonia occurred most frequently, and usually was extensively scattered throughout both lungs. The areas of infiltration were often confluent so that extensive consolidation resulted. The cut surface of these lungs presented a characteristic appearance which was peculiar in the large amount of exuding serum and blood. The influenza bacillus was frequently recovered at autopsy in pure culture from the lungs with this type of bronchopneumonia. Other organisms were also found and probably this type of pneumonia was produced by various

organisms on top of the initial lesions produced by the pandemic disease. Patches or considerable areas of lobar pneumonia were frequently found, due probably to some one of the pneumococci. Actual necrosis of the lung and abscess formation have been reported. The healing of these various lesions took place by resolution or organization of the exudate. Dilatation of the bronchi with areas of infiltration of the lung tissue about them were quite common and the escape of air into the interlobular tissue of the lungs occurred as a complication, but it was not settled under just what circumstances these complications occurred. All sorts of combinations of lesions occurred and several different organisms were recovered at autopsy from the different lobes of the lung in the same individual. Although a lesion in the smaller bronchi and in the alveolar wall was produced by the etiologic agent of the pandemic disease, the appearance of a pneumonia, whether broncho or lobar in type, usually signified invasion with some other organism.

In the pleural cavity various lesions were found which it was assumed were due to secondary invading organisms. Simple fibrinous pleurisy, serous effusions, seropurulent effusions and empyema, free or incapsulated, occurred. In some cases numerous small pockets of pus separated by organizing connecting tissue were encountered. Various organisms have been recovered from these different conditions. In some rare instances air ruptured from the interlobular connective tissue into one or both pleural cavities producing a pneumothorax. In the pericardial cavity serous effusions, fibrinous exudates and collections of pus have been reported. These were undoubtedly all due to various types of secondary invading organisms.

Empyema of the sinuses connected with the upper respiratory tract was frequently found as well as suppuration in the middle ear and mastoiditis. Infection of the parotid glands has been reported. The bacteriology of these complications has been quite varied. General peritonitis has been reported and abscesses in the subcutaneous and muscular tissues from both of which various types of bacteria have been recovered presumably secondary invaders. The hemorrhagic lesions produced in the muscles by the virus which produced the pandemic disease probably were a factor in the formation of the abscesses.

The period of incubation of the disease has been reported as one or two days by Keegan,²³ and as two days by Bloomfield and Harrop.²⁴ It seems pretty well established that the disease can develop as quickly as this, but whether it did in all cases is not so certain.

In considering the symptoms of this pandemic disease it is important to separate the symptoms which were due to the uncomplicated disease from those which were dependent upon the complications. The symptoms varied in their severity and in the number which

appeared in an individual case. The suddenness of the onset of the symptoms was striking. In many cases the transition from perfect health to marked prostration occupied only a few hours. The severity of the prostration was often marked. In addition to the prostration muscular pains throughout the body, headache, chills or chilly sensations, and nausea were usually present. Vomiting and diarrhea sometimes occurred. Usually coryza was met with at the start, but this and the appearance of the cough was delayed for one or two days in some cases. Cough, dry, tickling throat, sore-throat and hoarseness were also common symptoms. The patients frequently complained of nose-bleed, and it was quite common for menstruation to appear prematurely.

Upon examination the patient usually showed reddened conjunctivæ and pharynx. Fever was usually present. There was sometimes pallor but more commonly cyanosis was present even before any evidence of involvement of the lungs appeared. In some cases an erythematous rash suggesting measles appeared, in others purpuric spots and petechial hemorrhages occur. Lucke, Wight and Kime²¹ reported the appearance of papules and vesicles which contained a slightly turbid fluid. Signs suggestive of meningeal irritation were frequently seen, and Stangl²⁵ reported a considerable number of such cases in his group. The spleen was occasionally palpable. Except for these signs the physical examination was essentially negative.

The usual routine clinical pathologic tests were negative except for a white blood count below the normal. Matz⁸ found an elevation of the blood urea whether or not a complicating nephritis was present. He also claimed that some degree of acidosis occurred because the carbon dioxide tension in the blood was found diminished.

In many cases after a few days the fever subsided and the symptoms gradually disappeared. In a considerable number of cases, however, after a drop in the temperature about the second or third day, it became elevated again. This second elevation of the temperature in most cases signified an extension of the process into the lung with a beginning bronchopneumonia. It has not been definitely established whether this secondary rise in temperature always signified an invasion with some complicating organism or whether it was due simply to the extension of the existing process. At this stage of the disease the cyanosis usually became somewhat more pronounced. Upon physical examination in some cases there was no change in the chest signs, but usually signs of infiltration into the lung tissue began to appear. These varied from slight dulness or a few rales at some point over the chest to evidences of definite consolidation. In many of the cases evidence of infiltration of the lung tissue on both sides was found. As the process in the lung was an extension from a diffusely scattered lesion in the bronchi it was natural that the signs were found in both lungs. If one will remember

that the initial lesion started in the bronchi and the air spaces immediately surrounding them, one will appreciate that the lesions might be quite far removed from the chest wall. Therefore it was not strange, as Christian²⁶ pointed out, that the infiltration of the lung might be quite extensive before signs appeared.

In the cases in which the signs simulated a lobar pneumonia it must be remembered that the pathology of the condition showed frequently a confluent bronchopneumonia which gave the clinical signs similar to a lobar pneumonia. In these cases it was quite common for the character of the lung signs to change frequently not only from day to day, but often from hour to hour, so that at one time upon examination of the chest the signs suggested pleural effusion, at another a definite lobar pneumonia and at still another a bronchopneumonia.

In the cases in which some type of pneumonia developed a fatal termination occurred within a few days or the pneumonia dragged along for some time before recovery or death took place. In certain cases after the toxemia of the pneumonia had apparently been overcome the patient continued to be cyanotic and the case went on to a fatal termination with the appearance of suffocation from mechanical obstruction in the bronchi, so that air could not reach the lungs in sufficient quantity to carry on proper oxygenation of the blood. In those cases which recovered, however, the temperature dropped suddenly by crisis, as is seen in an ordinary lobar pneumonia, or it gradually returned to normal, as is seen usually in bronchopneumonia. This probably depended upon which type of secondary invading organism was present and also upon the character of the lesions produced in the lung. During this stage of the disease the leukocyte count remained low or it became gradually elevated. Even in the cases in which the pneumococcus has invaded the lung as a secondary invader the leukocyte count sometimes remained below normal throughout the disease.

A peculiar complication occurred in a few of these pneumonic cases which was met more often in some localities than others, namely, the appearance of air in the subcutaneous tissues of the neck with subsequent extension. Preceding the appearance of the air in the subcutaneous tissues above the sternum and in the neck there was pain beneath the sternum. This was probably due to the forcing of the air through the connective tissue of the mediastinum. This pain usually disappeared upon the appearance of the crepitation in the subcutaneous tissues of the neck. From this point the air sometimes invaded the subcutaneous tissues over the whole surface of the body extending upon the face, down the arms and the legs. It would seem as though there must have been some valvular arrangement at the point along the respiratory tract at which the air escaped into the tissues for this air to have forced its way through the subcutaneous tissue rather to have passed out the bronchi and

trachea. It is interesting that it was exceedingly rare for the air to break through the pleural surface into the pleural cavity. This extension of air into the subcutaneous tissue was not in itself a dangerous complication, because recovery took place in some of these cases even after extensive distribution of the air subcutaneously. It was gradually absorbed from the tissues and disappeared.

Various other complications have been described. These complications were, as a rule, dependent upon the invasion of some secondary organism and usually presented the picture expected for the particular organism. No attempt will be made to go into these complications in detail, but simply an enumeration of the various complications which have been reported will be made as follows: ulcerative stomatitis, osteomyelitis, endocarditis, pericarditis, empyema, peritonitis, various types of pleurisy, icterus, tachycardia, thyroiditis, cerebral thrombosis, neuritis, subcutaneous abscesses, otitis media, infections of the accessory sinuses and orchitis. Chronic bronchiectasis with resulting invalidism has followed some of the pulmonary complications. Meninger²⁷ reports that all types of psychosis followed this pandemic disease, and Fell²⁸ calls attention to the need of a guarded prognosis because the outcome was often different from what was expected. Meninger²⁹ also studied cases of neurosyphilis in order to see what effect the epidemic had upon them, and found that early cases of neurosyphilis were unfavorably influenced by the disease, that the late cases were not affected and that in no cases was the condition improved by the disease. Fishburg³⁰ and Murphy³¹ brought out the fact that cases with tuberculosis stood the epidemic disease well and that the tuberculosis did not flare up following it.

No specific treatment has been recommended for this disease called influenza in the early stages before involvement of the lung has taken place, except the use of vaccines. Even the use of vaccines has been applied chiefly to the treatment of complicating pneumonia and therefore will be discussed later. Emphasis has been placed upon the importance of rest in the early stages of the disease and some reports suggest that in those instances in which the patients were promptly put to bed upon the first appearance of the disease pulmonary complications were less liable to develop. Carefully controlled statistics, however, in this regard are not available and comparison between the results obtained in different localities are quite unreliable. In view of the tendency for invasion of the lungs with various bacteria attempts to kill off organisms in the mouth have been made. For this purpose a mouth wash and spray, including quinin, has been recommended in an attempt to kill the pneumococci present in the upper respiratory tract. In some places all streptococcus carriers have been isolated from other patients in order to prevent the spread of this secondary invader. Herrick³² has suggested that the edema of the lungs might be

diminished by the use of digitalis and venesection. On the other hand Keaton and Cushman³³ consider that death in these cases was the result of shock, and they considered that bleeding added to the possibility of shock. Breen, Bolling and Casper³⁴ recommend the use of coagulants to check the hemorrhage from the injured pulmonary vessels into the alveolar spaces. Tunncliffe¹³ recommends the administration of horse serum in order to stimulate leukocytosis. Cowie and Beavan³⁵ tried out adrenalin on the ground that there was a marked adrenal insufficiency in these cases without beneficial results. Therefore for the prepneumonic stage of the disease, rest, supportive treatment, forcing of fluids and diligent cleansing of the mouth are about all that can be done.

For the pneumonic stage of the disease, irrespective of whether this was produced by the etiologic factor of the disease itself or was dependent upon the secondary invasion of some complicating organism, various forms of treatment have been suggested. It was impossible to decide in many cases whether the pneumonia was the result of some complicating organism or not. If the leukocyte count in the blood was elevated some complicating organism was probably present, but if it remained low this test did not help differentiate, because pneumonias due to various organisms occurred, with low white blood counts. Examination of the sputum was done, but if organisms were found it was only suggestive that they were responsible for the pulmonary lesions. If the No. 1 pneumococcus was present in the sputum from the lungs the antipneumococcus serum against this organism was used. If this organism was not present the use of serum from patients convalescent from so-called influenzal pneumonia was tried in some communities. McGuire and Redden³⁶ first presented the results of the use of serum from convalescent patients, and their figures were so favorable that considerable impetus was given to this form of treatment. Redden³⁷ has more recently published the results of the use of this serum from patients who have recovered from an influenzal pneumonia and compared its use with the results from other types of human serum. He found that in order to be most effective the serum should have been collected from several patients who have recovered from a pneumonia. Stoll³⁸ has also tried out a variety of serums, and feels that the only one which was of any value was the one from patients who had recovered from so-called influenzal pneumonia. It must be realized that it was not definitely established just what was the cause of the pneumonia in the patients from whom the serum was collected. Therefore the specificity of the serum in relation to the cause of the pneumonia in a given case was uncertain.

The figures from the reports of McGuire and Redden³⁶ in the work done at the Naval Hospital in Chelsea show less mortality than most of the other reports from this part of the country, but attention must be drawn to the fact that not only the mortality

from this disease and its pulmonary complications varies considerably in different localities but even in the same locality at different stages of the epidemic. Therefore too much reliance must not be placed upon the results obtained from one hospital, especially when these results were not carefully controlled. Lord,³⁹ working at the Massachusetts General Hospital, and Locke,⁴⁰ working at the Boston City Hospital, have reported a small series of carefully controlled cases in which the serum from convalescent human patients was used as a therapeutic agent without any favorable results. Great caution must be used in giving credit to any special agent for apparently miraculous cures in those cases of pneumonia associated with this disease, because cases desperately ill have been observed in which recovery has occurred without any specific treatment. The opinion of the medical profession at present is considerably divided on the question of the therapeutic value of the serum from convalescent patients who have had influenzal pneumonia. It seems as though the enthusiasm for this form of treatment is diminishing. The author has never seen any benefit from the use of this serum, and is not in favor of its use.

Vaccines have been tried therapeutically for the various types of pneumonia associated with this disease, and also early in the course of the pandemic disease itself, with the idea of diminishing the number of cases of pneumonia. Koons⁴¹ found the results satisfactory, but the use of vaccines was not sufficient or under enough control to form any opinion of their value. If a vaccine were used it was usually made up from several strains of the pneumococcus, one or more of the streptococcus and the influenza bacillus. The use of a typhoid vaccine intravenously was also tried without any striking results.

The injection of glucose intravenously in influenzal pneumonia has been recommended by Koons⁴¹ and by Wells and Blaukinship.⁴² They consider it was beneficial but without any specific reaction against the disease, and it must be given repeatedly. Until the value of some one of these so-called specific therapeutic agents has been more definitely established, one is justified in limiting the treatment of these complicating pneumonias to general supportive measures and the use of digitalis. The use of Type I antipneumococcus serum for those cases in which the complicating organism is the Type I pneumococcus is the exception.

The prognosis in this pandemic disease for the cases in which there were no complications or pneumonias was good. The incidence of pneumonia varied considerably in the different localities and with the stage of the epidemic. In the early stages of 1918 complicating pneumonias were reported in about 20 per cent, of the cases, and of these cases about 30 per cent. died, making a total mortality of about 6 per cent. for the disease, as practically all the fatalities were from pneumonia of some form. Subsequent flare-ups of the epidemic,

however, have not been accompanied with so much pneumonia nor has the mortality from the pneumonia been so high. In pregnant women the occurrence of pneumonia was reported at one time to be more frequent and the mortality figures given by Harris⁴³ were much higher than among other people.

Considerable interest has been aroused in regard to the possibility of vaccination as a prophylactic measure against this pandemic disease and as a prophylactic measure against the development of pneumonia as a complication of the disease. On the assumption that the disease was caused by the influenza bacillus, and as the pneumococcus and streptococcus were frequent secondary invading organisms in the lungs, vaccines were prepared by combining cultures of influenza bacillus with the various types of pneumococci and streptococci. Individual reports have been made by Rosenow and Sturdivant⁴⁴ and others favorable to the use of these vaccines not only in preventing the disease but also in diminishing the amount of pneumonia and the fatalities from it. Most of the work with vaccines has been carried out in regions in which the disease was already present, and therefore it was impossible to carefully control the experiments. McCoy⁴⁵ and his co-workers succeeded in studying the value of a protective vaccine under careful control and found that not only it did not prevent the disease but also it did not influence the incidence of pneumonia or the mortality from it. McCoy perhaps sums up the situation most clearly in his statement that figures from uncontrolled experiments seem to suggest that the vaccine is of value, but carefully controlled experiments show that it is of no use. On the assumption that this disease was spread by the dissemination of the virus by means of droplets from the respiratory tract, elaborate measures to prevent the spread of the virus by the wearing of masks, etc., have been suggested and tried out not only among the ill and their attendants, but among the entire population of a community. The value of such procedure in the absence of carefully controlled experiments is quite uncertain, and the sense of protection given to the public, if erroneous, may be harmful. Therefore some doubt exists as to the value of such procedures with our present knowledge.

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ACUTE NITROBENZOL POISONING WITH STUDIES ON THE BLOOD IN TWO CASES.*

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It is apparent that certain people in this country will drink various harmful substitutes for liquor as a result of national pro-

* This is study No. 13 of a series of studies on the physiology and pathology of the blood from the Harvard Medical School and allied hospitals.

hibition. Scott and Hanzlik¹ have already called attention to a group of individuals poisoned in Cleveland by alcohol denatured with nitrobenzol and have suggested that intoxication from this substance may be seen more frequently in the near future than in the past. An additional case in Philadelphia, reported by Donovan² and two others, which were recently seen in Boston at the Massachusetts General Hospital, bear out the suggestion of Scott and Hanzlik and make it seem of interest to review the pharmacologic action of this product and the clinical features of cases which have absorbed it.

Nitrobenzol, or oil of mibrane, is a coal-tar derivative resulting from the action of strong nitric acid on benzol and having the chemical formula of $C_6H_5NO_2$. It is a pale yellow liquid which smells and tastes like oil of bitter almonds. Its history in relation to internal medicine is interesting. It was discovered by Mitscherlich³ in 1834, although it was not until 1859 that Caspar⁴ introduced it to the medical profession as a new poison with toxic properties. The first fatal case described in England was reported by Letheby⁵ in 1863. The first case described in America was reported by Stone⁶ in 1904. Since 1859, however, so many single cases or groups of cases have been studied by various observers that our present knowledge of the effect of this poison upon the body is fairly comprehensive.

Nitrobenzol, according to Thompson,⁷ is employed in the manufacture of high explosives and is used to a limited extent in perfumery, soap, confectionery and cookery processes in making dyes and in pharmaceutic laboratories. It is remarkable that a poison which is put to so many commercial uses should not be more toxic to people who handle it constantly. So long ago as 1863, however, Letheby remarked that "in every manufactory where nitrobenzole and anilin are prepared on a large scale the peculiar narcotic effects of these poisons are often observed. The vapors escaping into the atmosphere are breathed by the workmen and cause distressing headache and a heavy, sleepy sensation. For the most part these effects are not serious but are quickly relieved by fresh air and a mild stimulant, as a glass of brandy and water. Now and then, however, the workmen, from carelessness in their habits, expose themselves to the action of comparatively large quantities of these poisons, and then the effects are most dangerous."

In confirmation of this statement, Grandhomme⁸ in 1883 reviewed all the published cases in nitrobenzol poisoning up to that date and

¹ Jour. Am. Med. Assn., 1920, lxxiv, 1000.

² Ibid., 1647.

³ Poisons: Their Effects and Detection, Charles Griffin Company, 1906, p. 193.

⁴ Ibid.

⁵ Pharmaceutical Journal, 1863, Series 2, v, 130.

⁶ Jour. Am. Med. Assn., 1904, xliii, 977.

⁷ The Occupational Diseases, D. Appleton & Co., 1914, p. 342.

⁸ Die Thierfarben Fabriken, Koster, 1883, p. 17.

out of his series of 47 found only 4 which occurred in manufacture. Finally Miner⁹ has recently pointed out that although almost all shoe dyes contain large percentages of nitrobenzol, yet shoe dye poisoning is rarely seen. It thus seems evident that the people who handle nitrobenzol as part of their daily work are not the ones who suffer the serious casualties from it most commonly.

Another interesting impression obtained from a survey of the literature of nitrobenzol-poisoning is that large numbers of cases have occurred more or less together at two different times. Grandhomme found that the majority of his cases occurred a comparatively short time after nitrobenzol was first used commercially. Since 1883, the time of his publication, but few new cases have been reported until 1919. Since that date, Stifel¹⁰ has described 17 cases which were poisoned by nitrobenzol in shoe polish, Sanders¹¹ has added another case from the same cause, while Scott and Hanzlik, Donovan and the present paper have commented upon the group of cases which drank nitrobenzol as a substitute for liquor.

The pharmacologic action of nitrobenzol has been thoroughly studied. The most complete work upon the subject was reported by Filehne¹² at Erlangen in 1878. The most striking fact demonstrated by his experiments was that nitrobenzol kills by making the blood unable to transport oxygen. This occurred because the hemoglobin, in dogs at least, underwent a transformation from nitrobenzol into another form of hemoglobin having a characteristic spectroscopic absorption line which did not correspond to any of the ordinary hemoglobin products. Normal arterial blood if shaken outside the body with nitrobenzol did not show this change; on the other hand the blood of animals poisoned with nitrobenzol regained its power to take up oxygen after prolonged saturation with oxygen. Filehne's paper is of additional interest because of the deductions in regard to the treatment of nitrobenzol-poisoning drawn from his experiments. Aside from the obvious desirability of preventing this form of poisoning as much as possible, he suggested for the treatment of acute cases the transfusion of blood following copious bleeding.

The clinical appearance of cases poisoned with nitrobenzol is remarkably striking. One of the earliest English cases¹³ is quoted in detail as affording a clear description of the condition as well as on account of its historical interest.

"A woman, aged thirty years, tasted a liquid which had been used for flavoring pastry, and perceiving that it was very acrid on her tongue and lips, spat it out immediately and washed her mouth with water. She thought she could not have swallowed more than

⁹ Jour. Am. Med. Assn., 1919, lxxii, 593.

¹⁰ Ibid., 395.

¹¹ Ibid., 1920, lxxiv, 1518.

¹² Arch. f. Exper. Path. u. Pharm., 1878, ix, 329.

¹³ Quoted from Taylor: Guy's Hospital Reports, 1864, x, 193.

a drop, but in replacing the bottle she spilled about a tablespoonful on the table and did not immediately wipe it up. The vapor strongly impregnated the air of the small room in which she was, and produced a feeling of sickness in another servant. The burning taste in the mouth was immediately followed by a sensation of numbness and tingling in the tongue and lips and a strange feeling for the next hour. As the woman became worse, Mr. Fotherby was called in, and saw her in an hour and three-quarters after the occurrence. Her aspect was then quite typical of prussic-acid poisoning: The eyes were bright and glassy, the features pale and ghastly, the lips and nails purple as if stained by blackberries, the skin was clammy, and the pulse feeble. Her mind was then clear and she described how the accident occurred and what her sensations were. She was able to swallow a mustard emetic, after which she became rapidly worse, lost her consciousness, the teeth became set, the hands clenched and blue, the muscles rigid and convulsed. She vomited freely a pale fluid matter, which had the peculiar odor of nitrobenzol. The stomach-pump was used, but the fluid washed out of the organ had hardly any odor, owing, probably, to the small quantity actually swallowed and its removal by absorption. In about eleven hours there was reaction, consciousness returned and she was able to swallow. At the end of seventeen hours she was much better."

The striking points in this case and others are the slowness of onset of symptoms after exposure, the vagueness of symptoms until unconsciousness occurs but with gastro-intestinal symptoms and nervous symptoms being prominent, the characteristic color of the skin and mucous membranes and the rapidity with which return to normal occurs in patients who recover.

Letheby's pathologic report on his first fatal case gave an accurate account of the usual gross postmortem findings: "After death there were no appearances of convulsions but rather of narcotism and apoplexy. The face was flushed, the lips were livid; the superficial vessels of the body, especially about the throat and arms, were gorged with blood; the dependent parts were turbid; the blood was everywhere black and fluid; the lungs were somewhat congested; the cavities of the heart were full; the liver was of a purple color and the gall-bladder distended with bile; the brain and its membranes were turgid and there was much bloody serosity in the ventricles. Analysis discovered the existence of nitrobenzol in the brain and stomach."

The two Massachusetts General Hospital cases (W. M., No. 236170 and No. 236173) were both typical. They were young men who, in the course of a drinking party on April 13, 1920, bought six bottles of Jamaica ginger from a stranger. Both agreed that this ginger did not taste like ordinary ginger but was drinkable, so

that they partook freely of it. On subsequent analysis the liquid was found to contain a high percentage of nitrobenzol.

In about three hours after beginning on the first bottle one man began to have generalized headache, nausea, and blurring of vision. He thought that he fell on the sidewalk and remembered nothing further until he woke up in the hospital. The other man, at about the same time, began to feel dizzy and nauseated. He did not lose consciousness but came to the hospital with his friend.

At entry both men were of a steel gray-blue color, the unconscious man looking practically dead while his companion was of a ghastly color but in reasonably good shape. There was nothing else especially notable except that neither man excreted any urine for at least six hours after entry to the hospital. The stomachs of both men were washed out at once. The sicker man was bled 100 c.c. of blood and transfused with 600 c.c. of normal blood. In the middle of transfusion he suddenly woke up and appeared normal. The second man was also transfused, but with less dramatic effect. Both men, however, felt perfectly well on the following day and made normal recoveries, except that the more seriously poisoned man developed a mild, uncomplicated pneumonia.

The following laboratory studies were completed in both cases and are tabulated on page 544.

The most striking features in these tables are the hemoglobin figures. As can be seen the oxygen capacity of both bloods on the first observation was markedly reduced, in one case being only 6.2 volumes per cent. This figure approaches that obtained in one of Filehne's dogs, which was alive with an arterial blood having less than 1 volume per cent. of oxygen. The total hemoglobin in our 2 cases was not reduced, however. The fact that methemoglobin was not detected by spectroscopic examination suggests that a large proportion of the hemoglobin was changed to Filehne's nitrobenzol hemoglobin. This combination, in turn, was an easily destroyed compound as demonstrated by the blood analysis made twenty-four hours later. By this time the appearance of both patients was much more nearly normal and the bloods showed no diminution in their total hemoglobin, oxyhemoglobin or oxygen capacity. All cases, however, do not react this way, as many have been reported with unquestioned methemoglobinemia.

The leukocytosis which developed in one case has been described as occurring commonly in nitrobenzol-poisoning by Massini,¹⁴ but can scarcely be due to rapid blood destruction according to his opinion.

As both cases were anuric for six hours after entering the hospital it is of possible significance that the phenolsulphonephthalein test

¹⁴ Deutsch. Arch. f. klin. Med., 1910, ci, 72.

of one case should have only 20 per cent. forty-eight hours later. It is conceivable that nitrobenzol caused an acute toxic nephritis.

CASE I (NO. 236170) A.

Date, 1920.	Blood.							Urine.
	Red count.	White count.	Smear.	Hemoglobin, gms. per 100 c.c. blood.	Oxyhemoglobin, gms. per 100 c.c. blood.	O ₂ capacity venous blood volume, per cent.	Methemoglobin (spectroscope).	
April 13	5,072,000	40,000	Neg.	14.5	4.8	6.2	Not present.	High colored; contains para-amido-phenol; phenolsulphonaphthalein excretion 20 per cent. in two hours; total nitrogen in twenty-four hrs. 14.3 gm.; total urea nitrogen in twenty-four hours 12.2 gm.; total ammonia nitrogen in twenty-four hours 1 gm.; total acidity including ammonia as $\text{N}/10$ acid in twenty-four hours 832 c.c.
14	5,080,000	18,000	Neg.	15.2	14.9	19.9	...	
15	
20	5,008,000	10,800	Neg.					

CASE II (NO. 236173).*

Date, 1920.	Blood.							Urine.
	Red count.	White count.	Smear.	Hemoglobin, gms. per 100 c.c. blood.	Oxyhemoglobin, gms. per 100 c.c. blood.	O ₂ capacity venous blood volume, per cent.	Methemoglobin (spectroscope).	
April 13	4,204,000	10,800	Neg.	13.8	6.2	8.9	Not present.	High colored; contains para-amido-phenol; phenolsulphonaphthalein excretion 40 per cent. in two hours.
14	4,008,000	7,000	Neg.	15.2	14.9	19.9	...	
15	
20	5,040,000	10,800	Neg.					

* The total hemoglobin was determined by Stadie's¹⁵ method. The oxyhemoglobin was determined from the oxygen capacity by Van Slyke's¹⁶ method. We are obliged to Dr. W. Denis for recognizing para-amido-phenol in the urine.

¹⁵ Stadie: Jour. Biol. Chem., 1920, xli, 237.

¹⁶ Van Slyke: Jour. Biol. Chem., 1918, xxxiii, 127.

The high-colored, almost black urine excreted by these cases was probably due to para-amido-phenol. Meyer¹⁷ also recognized it in a case which he reported. There was nothing remarkable in the nitrogen metabolism on the one case studied nor was there any significant increase in the titratable acidity of the urine.

It so happens that the cases recently reported in America have been mild, although Donovan has laid stress upon the fact that nitrobenzol may prove a fatal poison. The literature on the subject, moreover, contains so many reports of fatal cases that due emphasis should be laid upon the mortality of 32 per cent. in the 47 cases reported in 1883 by Grandhomme and the mortality of 21 per cent. in the group of 15 cases which Adams¹⁸ discussed before the Association of American Physicians in 1912. Therefore, poisoning from nitrobenzol is a serious and often fatal condition.¹⁹

On the whole, nitrobenzol is by no means a new or rare form of poisoning but is of academic and clinical interest because of the effect it has upon the blood. Cases made ill by it in the past have absorbed it through the skin, by mouth and by inhalation; many accidental cases have occurred although this poison appears to have been less dangerous to those who handle it in their daily work than to those who have been poisoned through carelessness, curiosity, or the desire to commit suicide or abortion.

The symptoms and clinical picture of nitrobenzol poisoning are due to the fact the blood loses its function of transporting oxygen. Whether nitrobenzohemoglobin methemoglobin or both are constantly formed is uncertain. In any event, cases of nitrobenzol-poisoning complain of the gradual onset of nervous and digestive symptoms going on to coma and death and become a characteristic blue-black color. The blood of such cases shows no change in the total amount of hemoglobin while the oxygen capacity of the blood is remarkably diminished. The urine is almost black in color and contains para-amido-phenol.

The changed hemoglobin, as a rule, returns to normal hemoglobin quickly, so that oxygen can again be carried to the body cells in a short time. This fact probably explains why cases which look extremely sick can recover with surprising rapidity.

There is no specific or antidotal treatment for this form of poison-

¹⁷ Berl. klin. Wehnschr., 1905, xlii, 1353.

¹⁸ Tr. Assn. Am. Phys., 1912, xxvii, 503.

¹⁹ Since this paper was written, Dr. D. L. Edsall has called our attention to a fatal case of nitrobenzol-poisoning which came to the Massachusetts General Hospital in 1918. We are obliged to Dr. G. R. Minot for the following details in regard to the case: The patient, a man, aged forty-five years, was cleaning a railroad car with fluid which contained nitrobenzol. In some manner he broke the container so that its contents spilled over the lower half of his abdomen, soaking his clothes below the thorax. When he reached the emergency ward of the hospital, approximately forty-five minutes after the accident occurred, he was totally unconscious, intensely cyanosed and died in a short time. The impressive fact in relation to this case was that nitrobenzol absorbed through the skin caused death within almost a few minutes after exposure.

ing. Any nitrobenzol, however, which has not been absorbed in a given case should be removed from contact with the body as completely and quickly as possible. Bleeding and transfusion seem logical therapeutic procedures for the most severe cases.

A NEW INTESTINAL TUBE WITH REMARKS ON ITS USE IN A CASE OF ULCERATIVE COLITIS.

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ABOUT a year ago I¹ described an intestinal tube by means of which it is possible to reach the entire small intestine and also the large bowel for diagnostic and therapeutic purposes. The tube having a length of 15 to 20 feet, and being quite thin (8 mm. circumference), does not permit its employment for aspiration purposes. Inasmuch as it is not permissible to have more than 60 cm. of the tube enter the digestive tract, before the capsule end has passed the pylorus, it is absolutely essential to demonstrate by the roentgen ray the position of the tube before allowing its further passage into the alimentary canal. This is a great disadvantage, making the clinician absolutely dependent in his work upon the roentgen-ray apparatus. The handling of the very long tube is another cumbersome drawback. Ultimately the length of the intestine being subject to great variations the intestinal tube had to have a length enough to fit all occasions, thus frequently exceeding the actual need of the individual case.

In order to obviate these drawbacks I have constructed a "jointed intestinal tube." It consists of the usual duodenal tube, the distal end of which is provided with a metal fitting and a female thread. Several 1-meter long tubes of the same caliber as the duodenal tube (8 F.) are each provided with tiny metal fittings at both ends, on one side having a female and on the opposite side a male thread. All the threads are of exactly the same size and each male fitting can be joined with a female thread. The distal end of the new tube is formed by a piece of rubber tubing (20 to 25 cm. long and about 20 F. caliber), containing on its proximal side a metal fitting with a male thread and on its distal side a stopcock. This distal end-piece can be attached either to the first duodenal tube piece or to each subsequent length of tubing added, thus forming a "jointed tube." (See Fig. 1.)

The jointed intestinal tube² permits aspiration at one and some-

¹ Einhorn, Max: An Intestinal Tube, New York Med. Jour., September 13, 1919.

² The jointed intestinal tube can be obtained at Geo. Tiemann & Co., 107 East 28th Street, New York.

times 2 meter-lengths, thus making it possible for the clinician to ascertain the position of the capsule in the duodenum and thus facilitates its introduction. Each subsequent length of tubing is added when its predecessor has entered the digestive tract. In order to avoid curling up of the tube in the stomach it is essential not to allow too much tubing to enter the stomach while eating and to ascertain the position of the tube before adding another length. This is done by pulling the tube a short distance from the mouth, 2 or 3 inches. If there is no resistance felt the tube is curled in the stomach. If a resistance is experienced the probability is that there is no curling. At this point a roentgen ray is advantageous, as it shows the course of the tube more exactly. A roentgen ray will also be required to decide whether the cecum has been reached, whenever it is necessary to do so, in order to apply treatment to the colon.

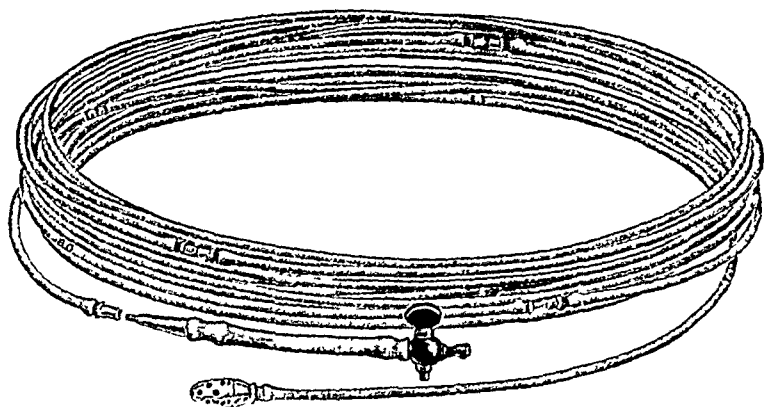


FIG. 1.—The jointed intestinal tube.

By means of the jointed intestinal tube the following case of probable ulcerative colitis has been successfully treated by lavage of the colon from above.

January, 1920. S. G., about forty years old, has been suffering for the last two years from severe diarrhea. Colicky abdominal pains are frequently present, especially before a bowel movement. Patient has lost considerably in weight and strength.

Present Condition. Examination of the chest does not reveal anything abnormal. The abdomen is slightly bloated, the liver a trifle enlarged and there is a distinct tenderness all over the colon on slight pressure. The gastric contents show: $\text{HCl} = +$; $\text{Ac} = 56$; no blood. The stool shows presence of starch, mucus and blood. The bead test reveals: beads appear in the stool after twenty-six hours; three-fourths of a potato, half fat, trace of thymus (no nuclei) present. Patient looks pale and complains of abdominal discomfort, lack of appetite and disturbed sleep. On an average he has six to eight movements during the day and four to six during the night.

Patient was then treated by me at the Lenox Hill Hospital for

a few weeks with tannin-agar, taka-diastase and a regulated diet, also bowel irrigations through the rectum, with some benefit, and sent to the mountains, where he stayed about two months. During May, 1920, patient returned to the city with an exacerbation of the previous symptoms.

A reëxamination showed practically the same findings as stated above. The diagnosis appeared to be severe ulcerative colitis. Inasmuch as the usual methods of treatment failed to accomplish the desired result, it appeared worth while to try washings of the bowel from above. Up to now for this purpose an appendicostomy or cecostomy would have to be first performed. With the intestinal

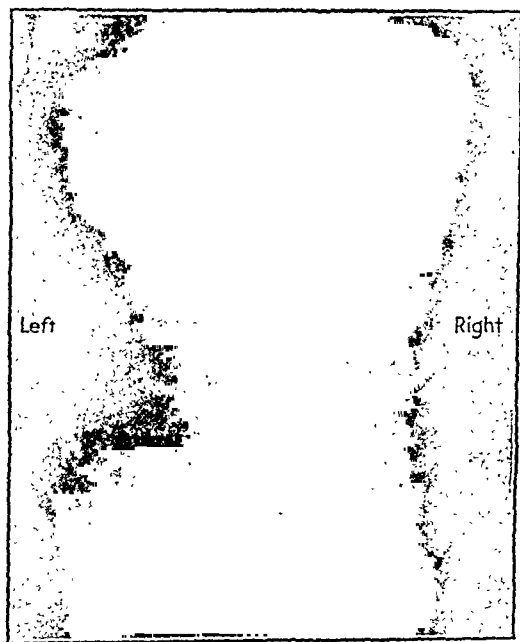


FIG. 2.—V 21, 1920. Roentgen-ray photograph of patient S. G., with the intestinal tube in the digestive tract. The capsule end of the tube is visible in the lower part of the duodenum.

tube at hand it was decided to try lavage of the colon from above by means of this instrument, thus obviating, if possible, the operation. Accordingly the jointed intestinal tube was introduced on May 20, 1920. As soon as the first part entered the duodenum (Fig. 2) the second joint was attached. On May 23, the third joint was added. A roentgen-ray picture showed the capsule end of the tube in the cecum (Fig. 3). Lavage of the intestine with a weak solution of carbonate of calcium (0.5 per cent.), employing a quart twice daily, was instituted as soon as the second joint had been attached, and kept up for about two weeks. Patient was nourished in the usual way by the mouth, partaking of the customary anti-

diarrheic diet. Soon after instituting this regimen the patient felt considerably relieved. The abdomen was not bloated, his appetite grew better and there were three or four movements daily. About a week later there were two or three movements daily, well formed, not containing any blood or mucus.

Wishing to have a roentgen-ray picture of the intestinal tube demonstrating the position of the entire intestinal tract, including the large bowel, a fourth joint was attached on the evening of June 5, 1920. The following day the capsule end of the tube appeared in the stool, hanging outside of the rectum. Desiring to demonstrate the location of the entire instrument with the capsule in the

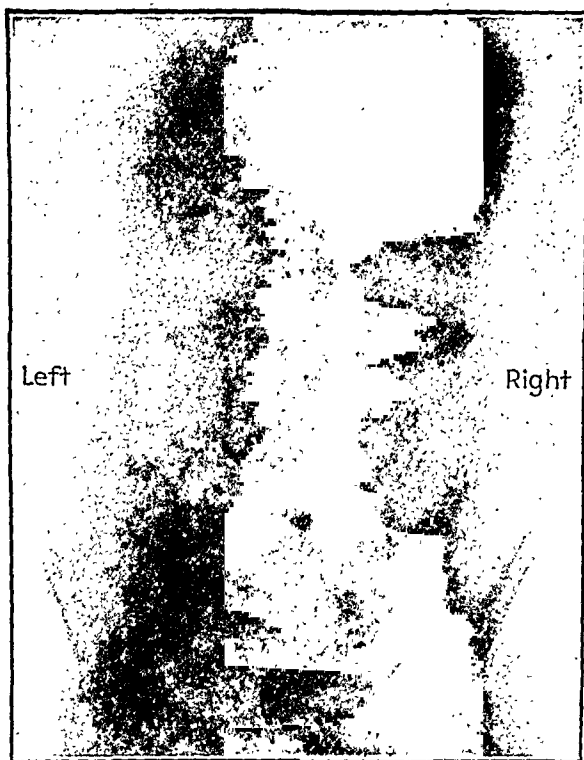


FIG. 3.—V 24, 1920. Roentgen-ray photograph of same patient shows the capsule end of the tube in the cecum.

digestive tract, I pushed it back into the rectum and had the patient roentgen rayed the following day, after injecting a bismuth mixture through the intestinal tube (Fig. 4).

In order to rid the patient of the instrument, the distal part with the stopcock was detached. The tube was tied tightly at the lips and allowed to slip into the stomach. Two days later (June 9) the whole tube appeared in the stool. During the entire time of treatment the patient experienced no pain or discomfort from the presence of this foreign body in his digestive tract.

It is thus evident that the intestinal tube can be used with advantage whenever this mode of treatment appears to be indicated.

In the case just reported the intestinal tube eliminated an operation—cecostomy or appendicostomy—which in similar instances is frequently done and effected great improvement—if not a cure.

Another point of interest regarding the penetration of the intestine by tubes is the rare event described by Dr. Palefsky,³ when the capsule-end of the duodenal tube (about 1 meter long), although the distal part was still at the lips, appeared through the rectum of a patient at the Montefiore Home. Palefsky explains this as string-

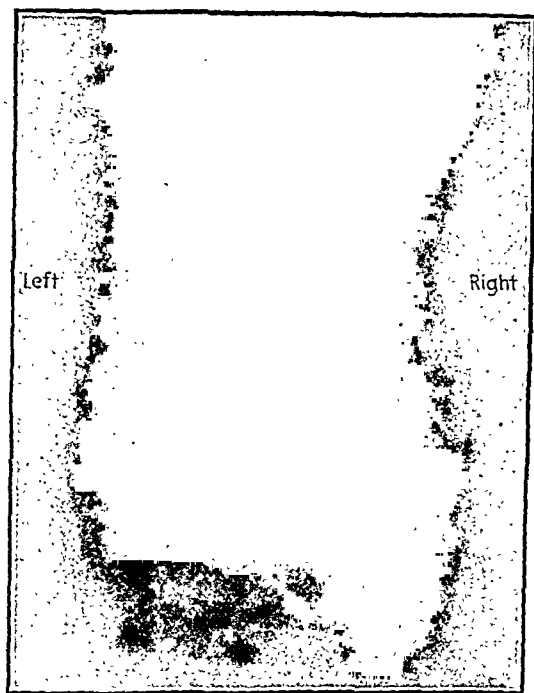


FIG. 4.—VI 7, 1920. Roentgen-ray photograph of same patient after filling the intestinal tube with a thin emulsion of bismuth. The whole course of the small intestine and colon down to the rectum is made visible by the tube. The capsule end is noticeable in the rectum.

ing up of the intestine over the tube. I have never seen a similar occurrence with the duodenal tube. Whether Palefsky's explanation is correct or whether there was a communication between the beginning of the small intestine and the colon (fistula), thus shortening the route is difficult to say. At any rate the duodenal tube cannot replace the intestinal tube, when in some instances a special diagnosis or treatment of the small intestine or colon is demanded. The jointed intestinal tube is, therefore, deemed of value.

³ New York Med. Jour., April 18, 1912.

NOCTURNAL POLYURIA.

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NOCTURNAL polyuria is a term designating an abnormal increase in the amount of night urine.

In seeking an explanation of its occurrence I attempted a review of the literature on nephritis which yielded no satisfactory explanation for the pathologic physiology of this symptom, and, above all, it revealed the fact that no special study of nocturnal polyuria has been made.

In health the amount of urine excreted during the hours of 8 A.M. to 8 P.M. is two or three times as much as is excreted from 8 P.M. to 8 A.M. When nocturnal polyuria exists the amount passed during the night hours exceeds that of the day, or it is habitually more than 400 c.c.

Here then is an interesting problem, Why should the normal relationship of function be reversed? Under what conditions does it occur? What are the peculiarities of the night urine? What is the diagnostic and prognostic significance of nocturnal polyuria?

Present Study. To this end I made a survey of 100 cases of sub-acute and chronic nephritis. These cases occurring in my private practice afforded me the opportunity of weekly observation. In some of them I made observations uninterruptedly for more than a year.

Methods. To establish the diagnosis in a case of nephritis aside from a study of the usual clinical evidences, when circumstances warrant, we make quantitative blood analyses for urea nitrogen, creatinin, blood sugar and chlorides. The phenolsulphonephthalein test is carried out both intramuscularly and intravenously. By this method we attempt to determine the tissue factor, *i. e.*, the rate of absorption by the tissues as well as the ability of the kidneys to eliminate the dye substance.

The urinalysis consists of a separate collection of the day and night urine from 8 A.M. to 8 P.M. and from 8 P.M. to 8 A.M. In these specimens, aside from the usual clinical and microscopic examinations, we make quantitative analyses of urea, chlorides, total acidity and ammonia. When the plasma chlorides are to be estimated a specimen of urine is obtained at the time when the blood specimen is taken for a quantitative chloride estimation.

While all this may sound formidable it is indeed very simple. The greatest tax is upon one's willingness to carry it over prolonged periods. Certainly, it is well worth doing because if properly interpreted much light is thrown on the patient's condition and it is the very best guide in our therapeutic efforts.

The urea estimation serves to indicate the protein metabolism; the chlorides indicate the salt intake and output, and the total acidity and ammonia indicate the acid equilibrium.

Cases Studied. In a survey of the entire series of cases upon which these observations were based, I find that from our present viewpoint they may be divided into three groups:

Group I includes those patients who come to the physician with no clinical symptoms of nephritis, and as judged by the usual methods, they show no evidences of impaired renal function. In most of them the time of onset of nephritis is unknown. The only evidences of an existing nephritis is the constant presence of albumin and casts. These cases show no nocturnal polyuria.

Group II includes those patients who have at least some unmistakable symptoms of early nephritis. These patients frequently show evidences of wear and tear. They give a history of periodic headaches, and at times we find the blood-pressure at the upper normal limit. Some of the patients in this group are anemic and present a picture of asthenia. In these cases the night urine is usually more than 400 c.c., but it does not always exceed the amount of the day urine.

Group III includes those patients in whom the diagnosis can be made with certainty on the clinical symptoms alone. They have enlarged hearts arterial changes; they suffer with nocturnal headaches, insomnia, dyspnea on exertion and they lack endurance. Usually they present a severe grade of arterial hypertension. It is in this type of case that we find an established nocturnal polyuria. The laboratory findings show defective renal function, as it is reflected in the blood analysis and by the various urinary examinations.

The Urinalysis in Nocturnal Polyuria. The amount of night urine may be from one and a half to four times that of the day urine. The color is darker in the day specimen and lighter at night. The specific gravity is high in the day specimen and low in the night specimen. The total solids eliminated is greater during the night when nocturnal polyuria is marked. These are the usual characteristics, and all of them are the reverse of the normal.

The Urea. In cases in which nocturia is present the urea concentration is greater during the day, but the total output is greater during the night. This is the reverse of that which is found when the kidneys are normal or but slightly damaged. It is an established fact that only the very seriously injured kidney will fail to eliminate urea or show a fixation of the urea elimination. From all my observations I should say that the ability of the kidneys to concentrate or eliminate urea is in no apparent way the cause of nocturnal polyuria.

The Chlorides. When nocturnal polyuria is marked the chloride concentration is higher at night, and since the volume is larger

the chloride output is also greater at night. In the normal person the chloride output is lower at night. The observations in this entire series show a distinct parallelism in the water and salt elimination, both tending constantly in the same direction. There is plenty of clinical evidence to show that polyuria is at times a result of chloride stimulation.

Total Acidity. The hydrogen-ion concentration as estimated by titration in the presence of neutral K oxalate and adding the ammonia value shows a higher acidity in the night urine when nocturnal polyuria is present. In the normal individual the total acidity is greater in the day specimen.

Concentration of the Urine. The one explanation which is most frequently offered for the occurrence of nocturnal polyuria is inability of the kidneys to concentrate urine. Most of my cases of nocturnal polyuria showed a distinct variation from time to time, the urea and chloride values often reaching quite a high point. On the other hand if nocturnal polyuria were due to inability to concentrate, both the day and night urine should be of the same low concentration. This, as all my observations show, is not the case at all. I am inclined to believe that nocturnal polyuria occurs because the diseased kidneys cannot eliminate water as well during the day as in the night.

Summary of the Urinary Findings in Nocturnal Polyuria. On all points excepting the higher concentration of urea during the day hours the night urine presents the characteristics of the day urine and the day urine resembles the normal night urine.

Therefore, when nocturnal polyuria is present we observe an almost complete reversal of function.

Blood Chemistry in Nocturnal Polyuria. We paid special attention to the blood chlorides in a series of cases in which nocturnal polyuria was a permanent symptom. In comparing the blood plasma chloride and urinary chlorides of these patients our findings seemed too indefinite for any reasonable deductions. The same may be said of blood sugars, creatinin and urea nitrogen.

Before offering an explanation of nocturnal polyuria let us summarize our evidence up to this point. In nocturnal polyuria the quantitative chemical analysis is the reverse of normal. The chief characteristics—those which are always present—are increased water output, higher acid concentration and output and lower urea concentration, but greater output in the night specimen.

Nocturnal polyuria occurs in subacute and chronic nephritis. It occurs when the blood-pressure is normal, but is more marked in arterial hypertension.

There are many possible factors which might influence the amount and character of the night urine, and I wish to discuss a few of the more obvious ones.

Foods and Liquids Ingested. Nocturnal polyuria occurs with the same regularity among patients who take their dinners at noon as those who take theirs in the evening. Neither the food nor the liquids taken during the evening are the cause of nocturnal polyuria, although much liquid taken in the evening does exaggerate this symptom.

Physical Exertion. Nocturnal polyuria occurs in patients who are at their usual occupations and in those who are away from their work. From these observations it appears that the total amount of physical exertion during the day is not the important factor. It is the variation between the exertion of the day and the relaxation of the night which undoubtedly does make the night a more favorable time for renal function when the kidneys have not fully accomplished their work during the day.

Blood-pressure. Nocturnal polyuria is most marked in nephritis with high blood-pressure. It occurs also when the blood-pressure is low. In borderline cases nocturnal polyuria disappears and the normal day and night proportions are reestablished when the previously high blood-pressure falls to normal. The alteration of pulse-pressure during the hours of sleep is probably the important factor in creating a more favorable condition for urinary filtration.

I see no reason why the renal epithelium should secrete better at night, but there seem to be many reasons why the altered renal circulation at night should prove more favorable to increased water elimination. Doubtless it may be that the unexcreted urinary substances of the day also act as a renal stimulant.

Posture. When a patient who has an established nocturnal polyuria goes to bed for a week or two the nocturnal polyuria continues irrespective of the fact that he is in the horizontal posture all of the twenty-four hours. During this bed period the nocturnal polyuria will be less marked, but the increased night urine will persist.

This brings us to what is perhaps the most important factor in the production of nocturnal polyuria.

Sleep. Up to this point our observations lead us to believe that it is not the heavy evening meal, nor the amount of physical exertion of the preceding day, nor the presence or absence of arterial hypertension, nor the horizontal posture which produces nocturnal polyuria. Having set these aside the one remaining factor which will come into our discussion is sleep. During the hours of sleep, when the muscular system is in a state of relaxation and the respiratory and circulatory systems are in a state of comparative rest, it must be that whether it is the lower pulse-rate or altered pulse-pressure, or whatever other alterations may occur in the mechanics of the renal circulation, the conditions are more favorable for renal filtration.

Summary and Conclusions. Nocturnal polyuria is a highly diagnostic symptom of an established subacute or chronic nephritis. It occurs independently of arterial hypertension. The quantitative

analyses show a complete reversal from the normal in the amount of work accomplished by the kidneys during the day and night periods.

Observations upon patients having nocturnal polyuria show that it is not the result of heavy evening meals, physical exertion, arterial hypertension nor the horizontal posture. The most probable cause seems to be found in the physiologic adjustments in circulation incidental to sleep. The evidences gathered in these observations suggest that nocturnal polyuria is primarily a manifestation of increased elimination of water because of a more favorable state of the renal circulation and that the increased elimination of salts is coincidental rather than causative.

THE WHITE ADRENAL LINE (SERGENT); ITS CLINICAL SIGNIFICANCE.

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SINCE the appearance of Sergent's American article¹ directing attention to his white adrenal line in 1917, considerable clinical application has been made of it in this country, to judge from the increasingly frequent references to it in the current literature.

This line is a blanching of the skin following light stroking by a blunt object, such as by the back of the finger-nail or the eraser at the end of a pencil. The subject assumes the recumbent position, with abdomen exposed for at least twenty minutes, and then a figure, such as a triangle or rectangle, is stroked lightly on the skin of the upper abdomen. Shading the part from bright light is of aid in the perception of the line. In about ten seconds a pure white band varying in intensity and unmixed with any element of red appears; it lasts from three to fifteen or more minutes.

Sergent definitely ascribes this phenomenon to a state of hypoadrenia.

Our interest in this remarkable skin reaction was aroused by studies made on a case of dystrophia adiposogenitalis² in which the line was present in a very pronounced degree. Curiously enough, while the line disappeared promptly following the administration of adrenalin subcutaneously, it reappeared quite quickly (in twenty

¹ The White Adrenal Line; Its Production and Diagnostic Significance, Jour. Endocrinol., January, 1917, i, 18.

² Unpublished; To be reported later. (Arch. Int. Med., 1921.)

minutes), in face of the fact that the general effects of adrenalin (tremor, cardiac palpitation, throbbing of vessels, increased pulse and heightened blood-pressure) were marked and persisted over a prolonged period (four hours).

These findings, inconsistent with Sergeant's explanation of the line, led us to investigate this phenomenon and the factors which influence it in a series of 255 cases.

In eliciting this phenomenon the directions set forth by Sergeant were followed in every detail.

Of the 255 instances, comprising all types of disease and a series of normals, a white line was obtained in 58 per cent.; a red line (*tâche cérébrale*) in 9 per cent.; an indifferent type of line as described by Tracey³ in 33 per cent. The latter is a deepening of the normal skin tint, with a whitish or reddish admixture, or a red quickly followed by a white band.

For purposes of comparison three grades of intensity were recorded, namely, one plus, two plus and three plus. Of the 145 instances (58 per cent. of total) of white lines, 14½ per cent. were three plus, 38½ per cent. were two plus and 47 per cent. were one plus.

It is interesting to note that the white line was the one most frequently found.

No difference was found in the response of the two sexes.

All types of disease were represented in this series (Table I).

Although the series analyzed is not a very large one the large number of normals revealing the line—58 per cent.—and the fact that 43 per cent. of the hypertension cases exhibited it, are of special interest.

It will be noted that the line was found in all instances of scarlet fever, hypopituitarism and in two cases of scleroderma.

Scarlet fever patients *quite constantly* reveal this phenomenon, a point emphasized by Moltchanow and Lebedeff.⁴

The typical white line response elicited in the skin, flushed with the exanthem of scarlet fever is not to be confused with the familiar momentary blanching produced by pressure of the hand. This blanching is very speedily followed by the return of the flush, whereas the white line appears after an "incubation period" of usually five to ten seconds, attains a maximum and slowly fades out.

After recovery from scarlet fever and the disappearance of the rash, this line disappears in a certain number of the cases.

Unfortunately we were unable to study a series of frank Addison's disease.

³ The Normal Reaction of the Skin to Stroking, Boston Med. and Surg. Jour., 1916, clxxv, 197. Correlations Between the Systolic Blood-pressure and Reflex Vasoconstriction (Anemic Dermography), Boston Med. and Surg. Jour., 1917, clxxvi, 15.

⁴ Vagotonus and Sympathicotonus in Scarlet Fever in Children, Roussky Vratsh, Petrograd, 1916, xv, 457; Abstracted in Jour. Endocrinol., January, 1917, i, 92.

Nor was it possible to correlate the presence of this line with any particular type of individual, *i. e.*, with respect to vasomotor system and nervous make-up, except that it seemed quite frequent in those with a hypertonic vegetative nervous system. As regards its relationship to endocrine disorders, its ascribed dependence upon a state of hypo-adrenia was certainly not demonstrated. It was not found that adrenalin-sensitive individuals bore any constant relationship to it, although they very frequently revealed it.

TABLE I.—THE INCIDENCE OF THE VARIOUS LINES IN DIFFERENT DISEASES AND NORMALS.

Disease.	Red.	Indefinite.	White.	Per cent. white.
Normals ⁵	1	12	18	58
Cardiovascular and cardionephritic	4	8	10	45
Anemias (including pernicious)	1	3	1	20
Neurological:				
Organic	2	11	18	58
Epilepsy	1	2	4	68
Functional and psychiatric	0	11	11	50
Tuberculosis (pulmonary)	3	4	18	72
Hypertension	3	5	6	43
Endocrine:				
Hyperthyroid	3	1	6	60
Hypothyroid	1	0	0	
Hypopituitarism	0	0	4	100
Hyperpituitarism	0	0	1	
Hypo-adrenia	0	2	0	
Eunuchoid	0	0	1	
Metabolic	1	6	1	12
Infectious	4	8	21	63
Scarlet fever	0	0	4	100
Measles	0	1	3	75
Neurocirculatory asthenia	2	0	3	60
Skin (miscellaneous)	0	3	5	62
Scleroderma	0	0	2	100
Arthritis, chronic, including arthritides deformans	3	5	2	20
Hypernephroma	0	1	0	

On the other hand, of particular significance has been the study of the age incidence (Chart I). It will be noted that the greatest incidence occurs between the ages of ten and thirty years. In fact the frequency of this line in young adults has been quite surprising; its infrequency in the extremes of life a matter worthy of attention.

Not only is this line most often found during young adult life, but it is met with most frequently in those with a normal blood-pressure. Infants with low pressure rarely have it. Yet a high systolic pressure, whether induced by the subcutaneous injection of tyramin or the result of hypertension does not preclude its presence; we have seen it in three individuals with systolic pressures of 230 mm. and over. No relation was noted to diastolic or pulse-

⁵ The majority of normals were young adults.

pressure variations. Pulse-rate has been found to have no bearing upon its presence.

On the other hand, it seemed that those individuals possessing a soft, doughy type of skin were especially likely to have the line.

The influence of various drugs, mechanical factors, etc., has been studied.

When adrenalin or pituitrin (posterior lobe hypophysis) are administered subcutaneously in doses of 0.6 to 1 c.c. the line disappears for usually a period of fifteen to thirty minutes, following which it reappears and quickly attains its former maximum. Not infrequently the other general effects of adrenalin (tremor, throbbing of vessels, cardiac palpitation, heightened blood-pressure, etc.)

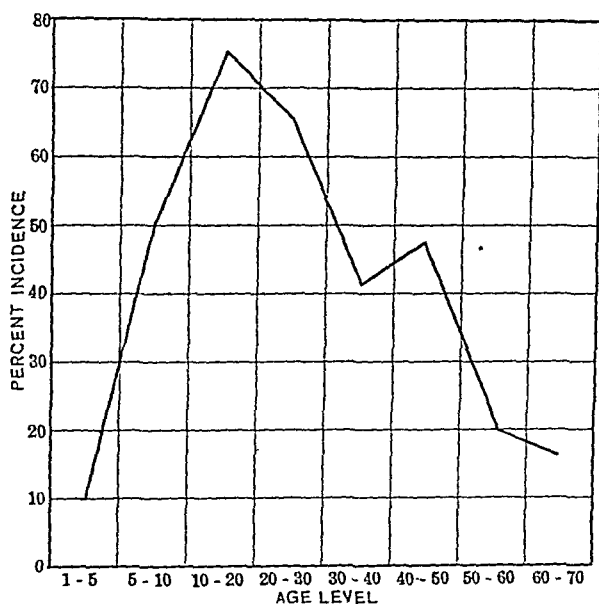


CHART I.—The percentage incidence of white line at various age levels.

continue over a considerably longer period than that occupied by the disappearance of the line. A characteristic example of this is herewith detailed (Table II).

This apparent inconsistency is to be explained, we believe, on the assumption that both adrenalin and pituitrin cause the disappearance of the line, solely by their peripheral vasoconstrictor action and not through any general effects.

In the same way the local application of heat and cold produce the disappearance of the line.

That the increase in blood-pressure has nothing to do with the line's presence or absence is again demonstrated by the action of tyramin, a drug which has been shown to produce extraordinary

risers of blood-pressure through splanchnic vasoconstriction and cardiac stimulation.^{6 7}

This drug in doses of 60 to 80 mgm. has conditioned rises of 60 to 100 mm. pressure without affecting the line.

TABLE II.—THE EFFECT OF ADRENALIN ON THE WHITE LINE IN A CASE OF HYPOPIUITARISM. (ADVANCED DYSTROPHY ADIPOSE-GENITALIS).

	Pulse.	Blood-pressure.		
		Systolic.	Diastolic.	
Before administration . . .	80	120	80	
Epinephrin, 1 c.c. 1 to 1000 solution(hypodermic):				
5 minutes later . . .	104	140	80	Tremor fairly marked; heart thumping; palpitation marked; patient moderately pale; respiration rapid; patient complains of feeling very nervous; disappearance of white adrenal line.
10 minutes later . . .	112	140	80	White adrenal line gradually reappearing and becoming more marked; marked tremor; palpitation of heart; nervousness continuing.
15 minutes later . . .	112	145	80	White adrenal line well marked, notwithstanding a maintenance of the heightened blood-pressure; tremor, etc., still marked.
25 minutes later . . .	115	140	80	White adrenal line still marked; blood-pressure still high.
1 hour 30 minutes later	110	145	88	White adrenal line marked; tremor; palpitation; throbbing and nervousness marked.
2 hours 30 minutes later	120	135	88	White adrenal line marked; palpitation and throbbing of vessels still fairly marked; patient still complains of nervousness.

Pilocarpin in doses of 6 to 8 mgm. seemed to accentuate the line in some cases; in others it seemed to have no effect (Table III).

In a group of 20 cases the effect of acute fatigue was noted. Running for varying distances, 150 to 300 or more yards, until considerable dyspnea and fatigue were manifest, was used. In

⁶ Hewlett, A. W.: The Action of Tyramin on the Circulation of Man, Arch. Int. Med., 1918, xxi, 411.

⁷ Hewlett, A. W., and Kay, W. E.: The Effect of Tyramin on Circulatory Failure during Infections and during or after Operations, Jour. Am. Med. Assn., 1918, lxx, 1810.

no instance was any appreciable change noted in the line, nor were we able to produce this line by this or any other method in an individual not possessing it before.

TABLE III.—THE EFFECT OF PILOCARPINE ON THE WHITE LINE IN A CASE OF MILD HYPOPIUITARISM.

	Pulse.	Blood-pressure.		
		Systolic.	Diastolic.	
Before administration	70	135	80	Moderate white line.
Pilocarpin, 8 mgm., by hypodermic:				
10 minutes later	80	135	75	White line more marked.
30 minutes later	80	130	70	A feeling of warmth noted; white line still marked.
50 minutes later	80	130	70	No perspiration; no special symptoms; white line marked on abdomen and face.

When the line is elicited in the standing position it is less prominent or absent.

We were unable to determine any changes in the line conditioned by psychic disturbances.

While the intensity of the line varied slightly at different times during the period of observation, no individual was found in whom the line appeared, having been absent, or in whom it disappeared when once present.

Tracy⁸ has postulated an attractive hypothesis, attempting to explain the appearance of the white and the red lines in different individuals, on the basis of a theory which is adapted from the work of Eppinger and Hess on Vagotonia.⁹

The theory may be formulated as follows:

1. Stimulus affecting the sympathetic nerve endings + adrenalin, acting on smooth muscles of vessels produces vasoconstriction (white line).

2. Stimulus affecting the autonomic nerve endings + hormone "X" ("autonomyn"¹⁰), acting on smooth muscle of vessels produces vasodilatation (red line).

This conception would imply that the white line is a manifestation of sympathicotonia, as Eppinger and Hess believe, whereas the red line is due to vagotonia.

Tracy¹¹ has even gone so far as to state that "reflex vasoconstric-

⁸ Loc. cit.

⁹ Vagotonia, a Clinical Study in Vegetative Neurology, Nervous and Mental Diseases Monograph Series No. 20, 1917. (Translated by Drs. Kraus and Jelliffe), Nerv. and Ment. Dis. Pub. Co.

¹⁰ A theoretical hormone elaborated by the thyroid gland, anterior lobe of the hypophysis and the thymus.

¹¹ Loc. cit.

tion (anemic dermatography) measures the adrenin content in the blood stream."

It will be noted that this conception is diametrically opposed to Sergent's belief, which would have the white line reflect a paucity of adrenalin in the blood stream.

Conclusions. 1. From the study of a series of 255 cases of a variety of diseases and normals, upon which numerous pharmacologic and other tests were performed, we feel justified in asserting that the so-called white adrenalin line of Sergent is a local vasomotor reflex, resident in the skin, bearing no direct relationship to adrenal gland activity.

2. The reasons for postulating the above are: (a) Its independence of blood-pressure, acute fatigue and other signs of hypo-adrenia; (b) its frequent occurrence in normals and in a variety of diseases unassociated with hypo-adrenia; (c) its reappearance in the face of persistent general manifestations of adrenalin subcutaneously administered; (d) its peculiar association with scarlet fever.

3. It would appear that the state of the vasomotor system which allows of its best exhibition is found in young adults of either sex, and especially in the exanthem of scarlet fever.

4. On the basis of the above series it may be stated that this line has not the clinical significance attributed to it.

5. In spite of the various hypotheses evolved regarding it, further work seems necessary to establish the exact physiologic mechanism of this remarkable vasomotor phenomenon.

Our thanks are due to Drs. Harlow Brooks, Sigmund Wachsmann and Robert Wilson for valuable advice and privileges granted. Through their courtesy we were able to study cases in the wards of the City Hospital (Blackwell's Island, N. Y.), Montefiore Home and Hospital and the Willard Parker Hospital, N. Y.

CHOLESTEROL IN CEREBROSPINAL FLUID.

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RECENTLY some importance has been attached to the presence of cholesterol in cerebrospinal fluid by Pighini¹ and by Hauptmann.²

¹ Ueber den Cholesteringehalt der Lumbalflüssigkeit einiger Geisteskrankheiten, Hoppe-Seyler's Ztschr. f. physiol. Chem., 1909, lxi, 508.

² Eine biologische Reaktion im Liquor Cerebrospinalis bei organischen Nervenkrankheiten, Med. Klin., 1910, vi, 181.

In view of this claim and in view of the role of blood cholesterol in various diseases we have made a series of determinations of cholesterol in cerebrospinal fluid, with special attention to pathologic fluids.

Methods.—The method of Bloor,³ with a few modifications, has been employed by us for quantitative determination and the method of Hauptmann² for qualitative determination. It should be noted here that although Hauptmann himself was not certain that the inhibition of saponin hemolysis by cerebrospinal fluid in some pathologic cases was due to the presence of cholesterol a comparison of the saponin with the Bloor method shows that with a few exceptions the two tests run quite parallel.

In the Bloor method the amount of fluid to be used for each test was naturally a question of great importance, as it was clear that cerebrospinal fluid could not contain as much cholesterol as blood contains.

After a series of experiments we found that whenever the cerebrospinal fluid contains cholesterol in appreciable amount, 3 c.c., the amount used for blood cholesterol will give a reading in the colorimeter. If 3 c.c. of fluid do not give a reading, 6 c.c. or even 10 or 15 c.c. of the same fluid will give no reading in the colorimeter. We therefore decided to take 3 c.c. as the standard amount of fluid, as one is usually able to spare this amount with ease. Whenever possible, however, 6 c.c. or more of the same fluid or of the same type of fluid were used as a check.

Three c.c. of the fluid which had been drawn by means of a spinal or ventricular puncture were measured into a 100 c.c. volumetric flask and ether-alcohol (1 to 3) added. The flask was heated to the boiling-point and set aside. After standing twenty-four hours to several days, ether-alcohol was added to the 100 mark, the contents filtered and 80 c.c. of the filtrate taken for the cholesterol determination. We found 10 c.c. of the filtrate, the amount used in the blood cholesterol method, insufficient for the determination of cerebrospinal cholesterol.

The filtrate was evaporated to dryness and the cholesterol extracted by chloroform and the chloroform extract concentrated to 5 c.c., which was then put into a 10 c.c. graduate, 2 c.c. acetic anhydride and 0.2 c.c. sulphuric acid added, shaken and put away for fifteen minutes in a dark place. The material was then compared with a standard of 0.5 mgm. of cholesterol in a Duboscq colorimeter if the color of the cerebrospinal filtrate were sufficient to make a reading. If no color at all appeared the solution remained light yellow and we called it negative. If a greenish-yellow color appeared we designated it as a trace.

³ The Determination of Cholesterol in Blood, *Jour. Biol. Chem.*, 1916, xxiv, 227.
The Determination of Cholesterol in Blood, *Jour. Biol. Chem.*, 1917, xxix, 437.

The technic of the Hauptmann test used was as follows: Each time the test was performed the hemolytic unit of saponin was determined. Various samples of saponin tried were found to vary greatly in their hemolytic action, but the sample finally used caused hemolysis in a 1 to 10,000 dilution. The dosage of this dilution necessary to cause complete hemolysis of 0.5 c.c. of a 7 per cent. suspension of washed sheep erythrocytes in 0.85 per cent. saline was determined by adding increasing amounts of the saponin solution to the corpuscle suspension in a series of small tubes. The hemolytic unit of the 1 to 10,000 saponin solution was usually found to be 0.3 c.c.; occasionally it was 0.2 or 0.4 c.c. After the saponin unit has been determined, 0.8 c.c. of cerebrospinal fluid to be tested was set up with the required amount of saponin and 0.5 c.c. of 7 per cent. sheep red corpuscle suspension. Control tubes with normal cerebrospinal fluid (one known not to produce any inhibitory effect on saponin) and with normal salt solution were also set up. The results were read after ten minutes in the water-bath at 37° and again after twelve hours in the refrigerator. The setting up of the saponin test with a positive result is illustrated by the following table:

Tube 1. 1 to 10,000 saponin, 0.3 c.c.; normal cerebrospinal fluid, 0.8 c.c.; 7 per cent. sheep corpuscle suspension, 0.5 c.c. Result: Complete hemolysis.

Tube 2. 1 to 10,000 saponin, 0.3 c.c.; cerebrospinal fluid to be tested, 0.8 c.c.; 7 per cent. sheep corpuscle, 0.5 c.c. Result: Inhibition of hemolysis.

Tube 3. 1 to 10,000 saponin, 0.3 c.c.; 0.85 per cent. saline, 0.8 c.c.; 7 per cent. sheep corpuscle suspension, 0.5 c.c. Result: Complete hemolysis.

Results.—We have examined 168 fluids for cholesterol; 74 of these were examined quantitatively, and of these 52 were also examined by the saponin method. The rest of the fluids were examined only qualitatively by the saponin method. Our fluids divided themselves into six groups:

1. *Normal fluid*, including all fluids in which the Wassermann, Lange, cell count and globulin tests were negative. These include a variety of conditions, such as pneumonia, multiple sclerosis, amaurotic family idiocy, epilepsy and other cases in which irritation of the brain justified spinal puncture but the fluid showed no pathologic findings; 88 fluids of this type were examined. Of these 24 were examined both quantitatively and qualitatively and 64 only qualitatively.

2. *Lutic or Neurosyphilitic Fluid*. This includes all fluids in which the Wassermann and Lange reactions were found positive. Of these 25 fluids were examined both quantitatively and qualitatively and 28 fluids only qualitatively.

3. *Meningitic fluid*, including all forms of meningitis. There were 16 fluids in this group examined both quantitatively and qualitatively.

4. *Brain tumor* (4 cases) and *brain abscess* (2 cases). Of the brain tumor cases a positive diagnosis had been made in 3 and a probable diagnosis in 1. The fluid from 2 of the positive brain tumor cases and from the one suspicious case were examined both quantitatively and qualitatively; that from 1 positive case only qualitatively. The fluid from 1 case of brain abscess was examined both quantitatively and qualitatively and the other only qualitatively.

5. *Hemorrhage of the Brain*. Two cases, both examined by both methods.

6. *Ventricular Fluid*. Three cases, both methods being used in each case.

Normal fluid gave no reaction at all with the Bloor method, no matter whether 3, 6 or even 10 c.c. were used; only when 25 c.c. of fluid was taken for a test was there a trace of cholesterol present. Saponin hemolysis was not inhibited by the presence of normal cerebrospinal fluid.

Lutetic fluid, with three exceptions, also gave no reading with the Bloor method nor was there any inhibition of hemolysis. Of the three fluids that contained cholesterol in appreciable amounts one was also meningitic in character. The two others were diagnosed merely as general paresis.

Of the fluid from cases of meningitis only three contained a sufficient amount of cholesterol to enable us to read it in the colorimeter, one of these also giving a positive Wassermann reaction. The rest of the fluids showed a greenish-yellow discoloration as the end reaction, which was taken to indicate the presence of a trace of cholesterol. There was not, however, a sufficient amount of cholesterol in them to allow a reading in the colorimeter. Saponin hemolyzed blood in the presence of meningitic fluid, although occasionally the hemolysis was delayed.

Brain tumor allowed no reading with the Bloor method, although a trace was present. In 2 cases saponin gave a partial or delayed hemolysis, also indicating a trace of cholesterol. In the other case no inhibition was present with saponin. One case of brain abscess gave a reading of 13 mgm. of cholesterol per 100 c.c. of fluid, but no inhibition of hemolysis took place. It may be interesting that the above case of brain abscess also had a meningitis which seemingly was terminal, as no meningeal symptoms were present throughout the disease. The cholesterol could not be due to the meningitis, however, as most cases of meningitis showed only a trace of cholesterol which could not be read in the colorimeter. Saponin caused hemolysis in the presence of the fluid from this case. The fluid from the other case of brain abscess was examined only for saponin hemolysis; hemolysis was delayed but not completely inhibited.

The 2 cases of hemorrhage of brain under observation both gave a large amount of cholesterol, the amount being 8 mgm. per 100 c.c. of fluid in one case and 17 mgm. in the other. In both cases there was complete inhibition of saponin hemolysis. The fluid in the latter case was removed from the ventricles of the brain and was yellowish in color. In the other case the fluid was removed by spinal puncture and was colorless.

Of the three ventricular fluids examined one was a hemorrhage of the brain, and, as mentioned above, gave a high cholesterol reading in the colorimeter (17 mgm.) and a complete inhibition of saponin hemolysis. The other ventricular fluid, which also gave a high cholesterol reading (103 mgm.) and complete inhibition of saponin hemolysis; was obtained from a premature infant with a marked hydrocephalus. The appearance of the ventricular fluid, the high cell count with the predominance of polymorphonuclear leukocytosis and a strong globulin reaction make the diagnosis of a meningitis certain, although the type of the meningitis could not be diagnosed, as no organism was isolated from the fluid. The great amount of cholesterol in the fluid makes one suspect the presence of a hemorrhage of the brain in the case.

The third ventricular fluid was obtained from a case of hydrocephalus and gave no reading in the colorimeter and no inhibition of saponin hemolysis. This last fluid shows that under normal conditions, *e. g.*, when there is no hemorrhage or meningitis, ventricular fluid contains no cholesterol.

Discussion.—In the older literature there is only an occasional reference to cholesterol in cerebrospinal fluid. Thus Schlossberger,⁴ Zdarek,⁵ Panzer⁶ and Coriat⁷ speak of the presence of cholesterol in hydrocephalus fluid. Of late four attempts have been made to study cholesterol in various types of cerebrospinal fluid systematically. Pighini⁸ found cholesterol in a large percentage of fluids of general paresis (88 per cent.), of epilepsy (66 per cent.) and of dementia precox (43 per cent.). Hauptmann⁹ found that saponin hemolysis is inhibited by cerebrospinal fluid from cases of brain and cord tumor (100 per cent.); hemorrhage of the brain (85.7 per cent.), tabes (83 per cent.), cerebrospinal lues (65 per cent.), multiple sclerosis (46 per cent.). He thought that the inhibition is due to the presence of cholesterol. Chaufford, Laroche and Grigant¹⁰ and Weston¹¹ found small amounts of cholesterol even in normal fluid.

⁴ Analyse von hydrocephalischen Flüssigkeiten, Arch. f. physiol. Heilk., 1851, x, 581.

⁵ Ein Beitrag zur Kenntniss der Cerebrospinalflüssigkeit, Ztschr. f. physiol. Chemie, 1902, xxxv, 202.

⁶ Zur Kenntniss der Cerebrospinalflüssigkeit, Wien. klin. Wchnschr., 1899, xii, 805.

⁷ The Chemical Findings in the Cerebrospinal Fluid and Central Nervous System in Various Mental Diseases, Amer. Jour. Insanity, 1903-4, lx, 733.

⁸ Loc. cit.

⁹ Loc. cit.

¹⁰ Le taux de la cholestérine dans de liquide cephalorachidien normal et pathologique, C. R. de Soc. de Biol., 1911, lxx, 146.

¹¹ Cholesterol Content of Cerebrospinal Fluid, Jour. Med. Research, 1915, xxxiii, 119.

Pighini determined cholesterol qualitatively by the Liebermann method, Hauptmann studied it by a serological method, while Chaufford, Laroche and Grigant and Weston determined it quantitatively.

The methods used by the above workers varied. Pighini used 25 c.c. of fluid and employed a tedious and complicated method. Chaufford, Laroche and Grigant unfortunately do not give the method they employed nor how much fluid they used. Weston worked with postmortem fluid in very large quantities, this method being open to criticism, on the ground that cerebrospinal fluid is known to undergo chemical and physicochemical changes post mortem.

Our results do not agree with those of Chaufford, Laroche and Grigant or with those of Weston, in that we found no cholesterol at all in normal fluids. Nor do our results coincide with those of Pighini, who found cholesterol in a very large percentage of fluids with a positive Wassermann reaction.

Our cases of brain tumor have been too few in number to express an opinion as to the accuracy of Hauptmann's statement. With the Bloor method there was only a trace of cholesterol in the two cases of brain tumor in which this method was used, and with the saponin method there was partial inhibition. The one case of brain abscess examined quantitatively gave a high reading of cholesterol in the colorimeter. There was, however, no distinct inhibition of saponin hemolysis, nor was there marked inhibition in the fluid from brain abscess examined only qualitatively.

Our results in hemorrhage of the brain agree with those of Hauptmann, there being a large amount of cholesterol with the Bloor method and complete inhibition of saponin hemolysis.

With minor exceptions the saponin method of Hauptmann agreed fairly well with the Bloor method, although the latter is more quantitative and more sensitive. This also shows that Hauptmann was right in his contention that the inhibition of hemolysis in some fluids is due to cholesterol.

The above results, we believe, show that the amount of cholesterol in pathologic cerebrospinal fluid depends wholly or in part on the degree of permeability of the meninges and has no specific pathogenesis. This is evident by the presence of a trace of cholesterol in all cases of meningitis and by the presence of large amounts in hemorrhage of the brain. It is also evident from our work that the claim of Pighini of the dependence of a positive Wassermann reaction on cholesterol has no foundation.

The usefulness of the cholesterol determination in cerebrospinal fluid for diagnostic purposes, we believe, is limited because of its presence in hemorrhage of the brain, in some cases of meningitis and also occasionally in general paresis. Still, its presence is corroborative evidence of the existence of a pathologic process producing increased permeability of the meninges. Whenever the

history of the case indicates it, hemorrhage of the brain should therefore be thought of, especially when large amounts of cholesterol are present.

Conclusions.—Normal cerebrospinal fluid contains no cholesterol or only a very small trace of cholesterol.

Fluid in which the Wassermann and Lange reactions are positive contains no cholesterol in appreciable amounts. Only three out of twenty-five such fluids gave a reading in the colorimeter.

Fluid of hemorrhage of the brain showed high cholesterol content.

Fluid from tumor of the brain gave a trace of cholesterol.

Fluid from a case of brain abscess gave a high cholesterol reading.

The majority of meningitis fluids showed a trace of cholesterol.

Three fluids had a high reading.

Ventricular fluid gave no cholesterol reading, except when there was the presence of hemorrhage of the brain or other pathologic condition.

The Hauptmann reaction seems to depend on the cholesterol content of the cerebrospinal fluid.

This work does not bear out Pighini's contention that the Wassermann reaction depends on the cholesterol of the fluid.

We believe that the cholesterol content depends wholly or partially on the permeability of the meninges.

CASES IN WHICH CHOLESTEROL WAS FOUND IN APPRECIABLE AMOUNTS BY THE BLOOR METHOD.

Name.	Diagnosis.	Quantity of fluid used.	Wassermann.	Cholesterol (Bloor) mgm. per 100 c.c.	Saponin.	Remarks.
P. P.	General paresis	6.0 c.c.	++++	13.3	Complete hemolysis	
Mixture	General paresis	10.0 c.c.	++++	6.2	Delayed hemolysis	
E. C.	Pneumococcus meningitis	3.0 c.c.	Negative	19.0	Inhibition in water-bath; hemolysis in twelve hours	Fluid drawn while patient was moribund.
M. N.	Tuberculous meningitis	5.0 c.c.	Negative	10.2		
S. S.	Meningitis	2.3 c.c.	++++	14.1	Type of meningitis undetermined.
L. P.	Cerebral hemorrhage	3.0 c.c.	Negative	8.0	Partial inhibition	
B. A.	Meningeal hemorrhage; meningitis	3.0 c.c.	Negative	17.0	Inhibition	Ventricular fluid.
B. S.	Hydrocephalus; meningitis; meningeal hemorrhage?	3.0 c.c.	Negative	103.0	Complete inhibition	Ventricular fluid.
J. C.	Brain abscess; terminal meningitis	6.0 c.c.	Negative	13.0	Complete hemolysis	Native amboceptor present.

PULSE-RATE AND BLOOD-PRESSURE RESPONSES OF MEN TO PASSIVE POSTURAL CHANGES.*

BY MAX M. ELLIS.

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THE development of the airplane has added interest to the circulatory response of men following passive alterations of body position, for the aviator is subjected frequently to sudden variations in body position, which are largely passive as far as his musculature is concerned. Changes in pulse-rate and blood-pressure correlated with changes in body position made by the subject, have been studied by many investigators, but the changes in circulation accompanying postural changes in which the subject is moved by some force outside of his body, have not received the same attention.

In experiments on animals Hill ('95) showed that the blood-pressure in the carotid artery was increased by tilting the animal from the horizontal to the head-down position and decreased by tilting from the horizontal to the head-up position. Barach and Marks ('13), working with young men fifteen to thirty years of age, on a tilting table, concluded that "when the element of muscular effort has been eliminated, change of body posture from the erect to the horizontal will cause an increase in the maximum pressure, a decrease in the minimum pressure and an increase in the pulse-pressure." Henderson and Haggard ('18) followed the circulatory responses in the head-down position of ten young men on the tilting board, and report that "in the inverted or head-down position (30 to 45 degrees) the heart-rate in ten men was slower than in the flat position by an average of 9.5 beats a minute and slower than the erect position by 17." Excepting two cases (in the tilt from the erect to the reclining position) all of the pulse responses were minus in the tilts which lowered the head and plus in those which raised the head. The responses in systolic and diastolic pressures were not so uniform. The systolic pressure of five of the ten men and the diastolic pressures of all ten fell on changing from the erect to the horizontal. On tilting from the horizontal to the head-down position the systolic pressure rose in some cases and fell in others, the subjects being about equally

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divided between the two responses. The same was true of the responses to the return tilt, *i. e.*, from the head-down position to the horizontal. The diastolic responses following both of these tilts were also about equally divided between plus and minus. Although the work of Stephens ('04) is not strictly comparable with the preceding articles because his subjects were not tilted except from the reclining to the head-down position, his averages of the responses in pulse-rate, and systolic-pressure to changes in body position are interesting in this connection. These averages show a decrease in the per minute heart-rate and an increase in the systolic blood-pressure from the erect position, through the sitting and reclining positions to the head-down position. Stephen's data were collected after the circulatory balance was reached by his subjects. More recently Barach ('19) summarizes the responses in pulse-rate, systolic and diastolic pressure of 48 normal adults to two passive tilts. When these subjects were tilted from the standing position to the reclining he found that the pulse-rate and diastolic pressure fell and the systolic pressure rose. Following the return tilt from reclining to standing position the pulse-rate and diastolic pressure rose and the systolic pressure fell.

These observations collectively suggest that the circulatory responses of men to passive tilts which lower the head are a decrease in the per minute pulse-rate, an increase in the systolic pressure (sometimes a decrease) and a decrease in the diastolic pressure (sometimes an increase).

The present study was undertaken at the Medical Research Laboratory of the Air Service with a view to obtaining additional data on the constancy of these responses of men to passive postural changes of various sorts and on the degree of these responses.

Fifty young men, twenty to thirty-one years of age, drawn from the medical department and from the air service of the army, were used as subjects. Each man was given the routine physical examination by an internist and by an ear, nose and throat specialist before selection for these tilt tests. No man not reported sound was taken. All of the subjects were familiarized with the tilting table and its operation before the tests were made, to eliminate the factor of surprise. During the tests the subject refrained from talking and the observers spoke only when necessary.

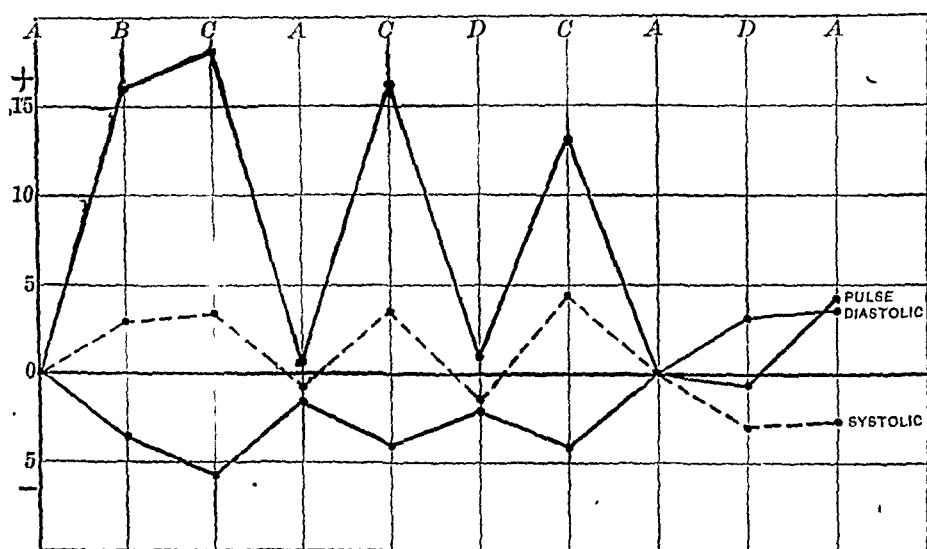
The tilting tests were made by two observers, one taking the pulse counts and the other the blood-pressure throughout the test. The subject was placed on the tilting table and swung up into the horizontal plane, here termed the reclining position, after the blood-pressure apparatus was attached to the left arm (a Tycos apparatus was used and the readings taken by auscultation) the subject was undisturbed ten minutes, when the first records of pulse and blood-pressure were taken simultaneously. Three readings were made and the averages taken as the normals against

which the subsequent readings in other positions were checked. As soon as the normals were established the subject was tilted quickly and quietly into the new position and a new reading taken. As assistants were always present to look after the mechanical side of the tilting the observers were able to make the first count of pulse-rate and the first measurements of blood-pressure within thirty seconds after the tilt. These figures have been recorded in the tables as the "immediate response." After the immediate response was recorded the subject was again undisturbed for five minutes. At the end of five minutes a second set of records were taken which have been termed the "response at the end of the fifth minute." These readings completed, the subject was tilted to the next position and the process repeated. Effort was made to take all readings at the end of expiration, but this was not always possible. From these several sets of readings the amount and direction of change in the pulse-rate and blood-pressures during the first thirty seconds after the body position was altered the amount and direction of change at the end of the fifth minute and the amount and direction of change during the five minutes in each position were obtained. In establishing these values the readings in a given position were compared with those taken at the end of the fifth minute in the preceding position. Five minute intervals were chosen because it was found by preliminary tests in which minute to minute readings were taken, that the subjects generally reached their maximum responses and adjustments to the new position within the first three minutes after the tilt was made.

Two series of tilts were used. In the first series the subject was tilted from the reclining position to head up 45 degrees, head up 45 degrees to standing, standing to reclining, reclining to standing, standing to head down 45 degrees, head down 45 degrees to standing. In the second series the first three changes of position were identical with the first three of the first series, *i. e.*, from reclining through head up 45 degrees and standing to reclining again. Then followed tilts from reclining to head down 45 degrees and head down 45 degrees to reclining (see *Chart*).

General Responses. Considering the responses in pulse-rate, systolic pressure and diastolic pressure separately, correlated only with the changes in the position of the subjects, the responses in pulse-rate were the most uniform of the three. Ninety per cent. of all cases in which the head was elevated during the tilt showed an immediate rise in pulse-rate and 84 per cent. had a higher pulse-rate at the end of the fifth minute after a tilt which elevated the head than at the end of the fifth minute in the previous position. The opposite tilts, those in which the head was lowered, gave much the same grouping of cases, with the opposite pulse response. Ninety-one per cent. showed an immediate fall in

pulse-rate on lowering the head and 86 per cent. had a lower pulse-rate at the end of the fifth minute than in the previous position. The predominant pulse responses, therefore, to all changes of position taken collectively were (1) an increase in pulse-rate—plus response—on raising the head, and (2) a decrease in pulse-rate—minus response—on lowering the head. All of the several types of tilts produced these responses, as from 62 to 100 per cent. of the cases in each tilt gave the responses designated above as the predominant responses. In the main these predominant responses were supported by larger percentages immediately after the tilt was made than at the end of the fifth minute, suggesting that the pulse response was compensatory to the sudden change



Average deviations in pulse-rate, systolic pressure and diastolic pressure from the reclining normals at the end of the fifth minute after each tilt. Tilts plotted in sequence used in the tests. Pulse-rate plotted in beats per minute and blood-pressures in millimeters of mercury: A, reclining; B, head up 45 degrees; C, standing; D, head down 45 degrees.

in position of a considerable volume of blood by gravity, and that additional responses during the next five minutes completed the adjustments to the new body position. This is confirmed by the changes in blood-pressure during the five-minute interval. In some of the tilts these readjustments amounted to a change in the character of the blood-pressure response from minus to plus. Although in other tilts this shifting of blood-pressure was not so profound, in all tilts excepting that from head down to standing more of the subjects showed a zero blood-pressure response at the end of the fifth minute than immediately after the change of position (Table I).

The blood-pressure responses were not so sharply grouped as were the pulse-rate changes. The predominant responses in

general, as indicated by the highest percentages, were a fall in systolic pressure and a rise in diastolic pressure following those tilts which raised the head; and a rise in the systolic pressure and a fall in the diastolic pressure following those tilts which lowered the head. The diastolic pressure varied in the same direction as the pulse-rate and the systolic pressure in the opposite direction. The predominant blood-pressure responses were supported by much smaller percentages than were the changes in pulse-rate. In several of the tilts the cases were about equally divided between plus and minus blood-pressure responses, indicating that the blood-pressure responses were much less constant than the pulse-rate changes.

TABLE I.—RESPONSES TO TILTS.

Tilt.	Cases.	Pulse.			Systolic.			Diastolic.		
		Rose.	Held.	Fell.	Rose.	Held.	Fell.	Rose.	Held.	Fell.
All tilts raising head .	244	90	5	5	17	9	74	58	7	35
		84	5	11	21	21	58	60	20	20
All tilts lowering head	108	8	1	91	48	9	43	18	8	74
		6	8	86	48	13	39	24	9	67
Head down to reclining	46	79	4	17	38	22	38	34	22	44
		69	14	17	38	18	44	47	23	30
Head down to standing	32	100	0	0	33	0	67	67	0	33
		100	0	0	17	17	67	83	0	17
Reclining to head up	58	100	0	0	4	4	92	82	4	14
45 degrees		100	0	0	18	14	68	76	10	14
Reclining to standing	50	100	0	0	12	8	80	68	4	28
		100	0	0	20	24	66	68	24	8
Head up 45 degrees to	58	79	17	4	14	7	79	41	4	55
standing		62	7	31	18	27	55	41	24	35
Reclining to head down	34	17	0	83	12	12	76	36	12	52
45 degrees		12	17	71	24	12	64	59	17	24
Standing to reclining	42	5	0	95	76	0	24	14	5	81
		5	5	90	71	5	29	19	5	76
Standing to head down	32	0	6	94	50	19	31	19	0	81
45 degrees		0	0	100	50	25	25	19	6	75

Data given in percentages for direct comparison. First line in each pair gives the immediate response as compared with the normal in the previous position; the second line gives the response at the end of the fifth minute after the tilt.

Three separate tilts did not follow the predominant responses of blood-pressure as determined by the mass data of all classes. In the reclining to head-down tilt the systolic responses of 76 per cent. of the cases were minus immediately after the tilt, and 64 per cent. held a systolic pressure lower than the reclining normal to the end of the fifth minute. The diastolic pressures of 52 per cent. also fell below the reclining value immediately after the tilt (the response expected from the predominant responses of the mass data of head lowered tilts), but in 59 per cent. of the cases of this tilt the diastolic pressure rose during the five-minute interval above the reclining normal. In the reclining to head-down tilt, therefore,

the pulse response followed the typical response of all head-down tilts, the systolic pressure fell instead of rising and the diastolic pressure fell as expected immediately after the tilt but rose above the reclining value during the next five minutes. The other two exceptions to the predominant responses of the mass data were in the diastolic pressure responses. In both the head down to reclining and head up 45 degrees to standing tilts the immediate diastolic response was a fall in pressure below the former value, followed by a rise during the next five minutes. The diastolic exceptions in all three tilts, therefore, were all of one type, an initial fall regardless of the position from which the tilt was made, followed by a rise above the value in the preceding position during the next five minutes. It is to be noted also in this connection that in each of the three tilts in which the diastolic pressure did not follow the predominant response of the mass data the cases of each tilt were about evenly divided between plus and minus response. As is shown under the discussion of the degree of change in these three tilts the actual amount of change in pressure measured in millimeters of mercury was slight and the diastolic pressures in these three tilts may represent indifferent responses.

If the predominant responses in pulse-rate, systolic pressure and diastolic pressure, as determined in Table I by the largest percentage of cases in each tilt group, be summarized in a formula (P = pulse, S = systolic pressure, D = diastolic pressure), $P + S - D +$ represents the predominant responses of the largest percentage of cases to a passive tilt in which the head was raised, regardless of the initial position from which the tilt was made. Similarly, $P - S + D -$ represents the predominant responses of cases in which the head was lowered, excepting the tilt from reclining to head down. In this tilt the largest percentage of cases gave the $P - S - D +$ responses.

These three formulæ of responses from the mass data were applied to the actual records of each individual case to determine the degree of correlation existing between the three responses of pulse-rate and systolic and diastolic pressures. The responses at the end of the fifth minute after the tilt were used (Table II). Only one-third of all cases in which the head was elevated during the tilt gave the expected responses in all three variables, pulse-rate, systolic and diastolic pressures. In the tilts lowering the head the percentage was slightly higher but still below 50 per cent. In only two tilts did the percentages of cases agreeing with the formula of responses exceed 50 per cent. in the head down to standing tilt and in the reclining to head up 45 degrees tilt. Cases giving any two of the predicted responses were more numerous, including 50 per cent. or more of the subjects in each tilt with the exception of the head down to reclining tilt. A comparison of the cases giving any two of the expected responses suggests there is little difference

in the constancy of the systolic and diastolic blood-pressures, as the *PS* and *PD* groups were about the same. Fewer subjects gave both of the predicted blood-pressure responses than gave the predicted pulse and either one of the blood-pressure responses. This was excepted from the summary of the mass data (Table I) as the pulse-rate changes were the most constant of the three responses. This confirmation of the grouping in Table I gives added value to those percentages, which show not only the relative constancy of each response but also that the predominant method of compensation was a change in pulse-rate.

It is evident from Table II that the responses to changes in position were not equal in the three variables, pulse-rate, systolic pressure and diastolic pressure, and that there was no stereotyped response which included the majority of cases. Satisfactory compensations, at least such as would maintain the individual for five minutes without loss of consciousness (none of the subjects fainted during the tilts) were made by other combinations of pulse, systolic and diastolic responses than those expected from the mass data.

TABLE II.—CORRELATIONS OF THE THREE RESPONSES, PULSE-RATE (P), SYSTOLIC PRESSURE (S) AND DIASTOLIC PRESSURE (D). DATA IN PER CENT. OF CASES GIVING RESPONSES INDICATED.

Tilt.	P + S - D + Per cent.	P - S - Per cent.	P + D + Per cent.	S - D + Per cent.
Head down to reclining	13	30	39	26
Head down to standing	67	67	83	67
Reclining to head up 45 degrees	55	72	70	55
Reclining to standing	32	50	56	32
Head up 45 degrees to standing	21	48	27	30
All head up cases	33	52	50	38
	P - S + D - Per cent.	P - S + Per cent.	P - D - Per cent.	S + D - Per cent.
Standing to head down	31	50	70	31
Standing to reclining	38	57	62	43
	P - S - D + Per cent.	P - S - Per cent.	P - D + Per cent.	S - D + Per cent.
Reclining to head down	47	58	53	47

Degree of Response. In Fig. 1 the mean values of change in pulse-rate per minute and blood-pressure in millimeters of mercury have been plotted, taking the several tilts in the sequence in which they were made on the subject. The mean values were obtained after the actual values of all individual cases had been plotted by classes. As the pulse-rate counts were made in twenty-second units and multiplied by three a deviation of plus or minus one count by the observer has been allowed, and similarly a deviation of

plus or minus one unit (2 mm.) on the Tycos dial has been allowed in the blood-pressure readings. The zero class of the pulse values included, therefore, all cases whose responses varied from plus three beats to minus three beats per minute and the zero classes in the blood-pressure all from minus 2 mm. to plus 2 mm. The class ranges for pulse-rates were nine beats per minute and for blood-pressure 6 mm. of mercury.

The tilts from reclining to head up 45 degrees and from reclining to standing gave almost identical degree changes, being $P +16$ beats, $S -3.5$ mm., $D +3$ mm. and $P +16$, $S -4$, $D +3.5$ respectively at the end of the fifth minute after the tilt. When the standing position was reached by two tilts, *i. e.*, reclining to head up 45 degrees and head up 45 degrees to standing, greater deviations from the reclining normals of pulse-rate, systolic and diastolic pressures were obtained, the responses at the end of the fifth minute of standing after these two tilts being, $P +18$, $S -5.5$, $D +3.5$. These values equal or exceed each of the three responses to either the reclining to head up 45 degrees tilt or the reclining to standing tilt. When the standing position was reached by one tilt from the head-down position, *i. e.*, the head down to standing tilt the pulse response was smaller and the diastolic response greater than either of the other two standing values. The response at the end of the fifth minute of standing after the head down to standing tilt were $P +12$, $S -2$, $D +6$ and the deviations from the reclining normals $P +13$, $S -4$, $D +4.5$.

In the reverse tilts, standing to reclining, opposite responses obtained, $P -17.5$, $S +4$, $D -4$, so that the readings at the end of the fifth minute in the reclining position were almost identical with the normals taken in the reclining position. In the standing to head-down tilt the response in pulse was not as great as in the standing to reclining tilt being $P -15$, $S +2$, $D -5$. Although less than the responses from standing to reclining these values following the standing to head-down tilt are fairly close reverse responses to those following the head down to standing tilt. The responses after that tilt were $P +12$, $S -4$, $D +4.5$. It is evident that a subject does not relax as completely in the unusual position of head down 45 degrees as in the reclining position, and the factor of muscular effort, either conscious or unconscious, is not completely eliminated in the head-down position. Similarly a certain amount of muscular effort on the part of the subject cannot be avoided in the standing position even though the subject is brought to this position by forces outside of his body. In the head down to standing tilt, therefore, the muscular effort of the subject and the movement of the blood by gravity both contributed to the reactions of the subject.

In order to ascertain the responses to the head-down position following a tilt from a position in which the muscular effort of the

subject was eliminated as far as possible, part of the subjects were tilted from the reclining to the head-down position and then back to the reclining position. The responses at the end of the fifth minute in the head-down position following the reclining to head-down tilt were quite different from those at the end of the fifth minute in the head-down position following the standing to head-down tilt. Following the reclining to head-down tilt the deviations from the reclining normals were $P - 0.5$, $S - 4$, $D + 3$ at the end of the fifth minute as compared with $P + 1$, $S - 2.5$, $D - 1.5$ at the end of the fifth minute after the standing to head-down tilt. After the return tilt, head-down to reclining, the subjects did not return to the reclining normals in five minutes, the average deviations from the reclining normals being $P + 4$, $S - 2.5$, $D + 3.5$.

From these various degree values it seems that the subjects examined made rather complete adjustments in five minutes to tilts in the reclining-standing quadrant, as the changes in pulse and blood-pressure in one direction are offset by approximately equal changes in the opposite direction on reversing the tilt. In the reclining to head-down quadrant the responses were much less uniform, and the circulatory balance was probably not established in the five-minute interval. Tilts starting in the reclining-standing quadrant and ending in the reclining-head-down quadrant, or *vice versa*, gave more uniform and also more profound responses than tilts in the reclining-head-down quadrant alone. These tilts, however, which carried the subject through more than 90 degrees, showed the disturbing effect of the head-down position, either at the beginning or the end of the tilt, upon the general compensations of the body to changes in position.

Considering the mass data of all cases collectively the responses obtained from these fifty men were in general the responses expected from the review of previous experimentation. The formulæ $P+ S- D+$ for the tilts raising the head and $P- S+ D-$ for those lowering the head, included the largest percentages of responses in all tilts excepting the reclining to head-down tilt, the mass responses of which were $P- S- D+$. The application of these formulæ, however, to the individual cases showed that a relatively low percentage of the individuals actually gave these three responses simultaneously and that these formulæ were therefore unreliable for the study of individual subjects even among men who had been pronounced in good physical condition. The response to passive changes in body position, as evidenced by the data here offered, was primarily one of change in pulse-rate. The blood-pressure responses were much more subject to individual variation in the general adjustment following these passive body position changes, although the blood-pressure responses did show definite groupings in the mass data. As the effect of the shifting

suddenly of a quantity of blood by gravity could produce through its effect on the nervous mechanism controlling the heart, changes in pulse-rate such as followed the changes in body position, and as several other factors are involved in the blood-pressure changes, a greater constancy of the pulse responses might be expected.

The responses in systolic pressure to the reclining to standing tilt were so different from those given by Crampton ('13), for healthy men on standing from the reclining position that the mass data may be reviewed here for comparison. Crampton states "that in the perfectly normal there occurs upon rising from the recumbent position a vasoconstriction effort which squeezes these veins (splanchnic) and raises the blood-pressure, which more than overcomes the hydrostatic load." In the tilt from reclining to standing the mass response was a fall in systolic pressure, supported by 80 per cent. of the cases immediately after the tilt, and by 66 per cent. at the end of the fifth minute, instead of the rise in systolic pressure found by Crampton in the men who stood voluntarily. As the subjects used in these tilting tests had been reported sound by the examining surgeons the vasomotor tone of the subjects was presumably good. The fall in systolic pressure following the tilting of these men from reclining to standing suggests either a lag in this compensatory vasoconstriction effort or a greater demand for compensation than could be met by the splanchnic area alone. As the percentage of cases giving the fall in systolic pressure fell during the five-minute interval from 80 to 66 per cent. there was some compensation which raised the blood-pressure during the five-minute period in at least 14 per cent. of the cases. In the case of the individuals rising by their own muscular efforts the tightening of various muscles of the body which would occur in the act of rising, would in part prevent the fall in pressure which took place in the reclining subjects who were suddenly tilted into the standing position. The relative demand, therefore, for compensation from the splanchnic vessels would be greater in the case of the tilted subjects than in that of the subjects rising by their own muscular effort.

Summary. 1. In general tilts elevating the head gave a rise in pulse-rate, a fall in systolic pressure and a rise in diastolic pressure, and those lowering the head a fall in pulse-rate, a rise in systolic pressure and a fall in diastolic pressure. The conspicuous exception to these responses was the reclining to head-down tilt in which the largest percentage of cases gave a fall in pulse-rate, a fall in systolic pressure and a rise in diastolic pressure.

2. The individual data showed that only a little over one-third of all cases gave the three responses in pulse-rate, systolic and diastolic pressures expected from the mass data, simultaneously.

3. Tilts from reclining to head down 45 degrees and return gave the least constant responses of all the tilts used.

4. The tilt from reclining to head up 45 degrees produced almost the same degree of responses as the tilt from reclining to standing.

5. With the exception of the tilts in the head down to reclining quadrant the responses given to any tilt were offset by approximately equal opposite responses when the tilt was reversed.

6. The initial and final positions of the subject had more effect on the degree of responses following a tilt than did the distance travelled by the subject during the tilt.

The writer wishes to acknowledge his obligations to Lieut. Harry Fried, M.C., who assisted in a large number of these tilting tests.

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LABORATORY AIDS IN THE DIAGNOSIS OF GONOCOCCAL INFECTIONS, WITH SPECIAL REFERENCE TO THE GONOCOCCUS COMPLEMENT-FIXATION TEST.

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THE present intensive campaign for the education of the general public in regard to the incidence, treatment and prevention of venereal diseases will, it is hoped, do much to lead to their early recognition, and, following upon this, and instructions as to their infectivity—which must, of necessity, form part of their treatment—great strides in their prevention are to be hoped for.

Indeed, it is now not an infrequent occurrence for those about to marry to seek information as to their freedom from venereal infection and because of this fact, and because, particularly in cases of long standing or those whose infection long antedates their visit to the doctor, the question as to their ability to infect others is a matter difficult to decide, a *resume* of the laboratory aids in the diagnosis of gonococcal infections seems timely.

In spite of the fact that the recognition of the typical case of gonorrhea is, as a rule, a matter of no difficulty, there are a number of cases of urethritis, especially in the female, where the diagnosis is not readily to be made.

A wrong positive diagnosis is an injury to the patient not readily

repaired; a wrong negative diagnosis may cause irreparable harm to the patient, his family and to the community, and every method available to avoid either error should be called upon whenever possible.

It is, of course, an obvious and admitted fact that not all cases can be recognized with absolute certainty by laboratory methods alone. There is always the latent case, the chronic case, especially in the female, in which bacteriologic evidence as to its origin is lacking; and in such cases, as in other conditions, the clinical evidence must be the deciding factor. However, in a certain number of cases specific evidence can be elicited if the proper methods are applied, and to call attention to these is the object of this paper. As always, it must be remembered that it is not the test but its interpretation which is of value.

Cases in which laboratory evidence of gonococcal infection is to be sought for may be divided into three groups: (a) Acute infections actually or suspected to be of gonorrheal origin; (b) cases in a chronic stage either with or without a history of previous acute infection; (c) cases which may be looked upon as presenting secondary manifestations of the disease, examples of which are arthritis in the male and salpingitis in the female.

Bacteriologic Diagnosis of Acute Infections. These may be accompanied by a history of diagnostic value, or this may be entirely lacking, as is usually the case in the female. In the male, as a rule, the presence of an acute, urethral discharge is preponderating evidence of gonorrhea; because, however, of the occasional case of non-specific urethritis, an error in the diagnosis of which may lead to dire results, a microscopic examination of the stained smear is indicated.

There are several points in the preparation of such specimens, minor details in themselves, perhaps, but all, in their summation, enhancing or vitiating the value of the examination.

1. The patient should not void for at least an hour previous to taking the specimen, thus avoiding flushing out of the canal.

2. The smear should be from the urethra. This is of particular importance in the female, for nothing is of less diagnostic value, except in the vulvovaginitis of children, than a hastily taken smear from the vagina. In the adult female additional preparations should be made from the cervix and so labelled.

3. The smear should not be too thick, as the difference between Gram-negative and Gram-positive organisms may be a matter of some difficulty to determine, because the thickness of the smears protects them from the action of the reagents.

4. The smears should be taken in duplicate upon microscopic slides or cover-glasses which should be allowed to dry spontaneously before being placed in contact. Nothing is more unsatisfactory than slides which have been placed together while moist, have adhered upon drying and must be pried apart for staining.

5. Douches, injections, washes and the like should not be used just prior to taking the specimens.

While the typical gonococcus is readily recognized by those familiar with its morphology, in the simple, single-stained preparation, such as Loeffler's methylene blue, the fact that many times they may not be typical in appearance and that there are other organisms which morphologically resemble them in appearance, renders the use of Gram's staining technic advisable as a routine.

Chief among the organisms morphologically resembling the gonococcus is the meningococcus, which, however, is not often found in the same localities; other organisms of more importance as being seen in urethral smears are coccoid forms of the colon bacillus, phagocytized cocci which, as a result, may stain indifferently, and the *Micrococcus catarrhalis*.

What are the criteria for the recognition of the gonococcus in the stained smear? It must be Gram-negative; it must be a diplococcus and typical bean- or kidney-shaped forms must be demonstrated in some area of the smear, and careful search should demonstrate some intracellular forms. In this connection it must be borne in mind that, in the acute discharges, the majority of the gonococci are not infrequently entirely extracellular.

These conditions, having been fulfilled in the presence of an acute discharge with or without a suspicious clinical history, suffice to render the diagnosis of gonorrheal infection justifiable.

The exact technic of Gram-staining deserves a word of mention, as it is the rock on which many stumble. There are several sources of error inherent in the method itself if minor details are not carefully attended to.

1. The gentian-violet solution made with anilin water must be relatively fresh, and even when other solutions of more stable character, such as Stirling's stain, are made use of the stain should be frequently tested with known Gram-positive organisms.

2. The film must not be too thick, as decolorization may be difficult and unsatisfactory.

3. The films should be allowed to dry spontaneously, and care should be taken to avoid overheating when fixing, as atypic staining may occur.

4. The iodine solution should be stronger than that in the original formula, the water being reduced from 300 c.c. to 100 c.c. (iodine, 1 gram; potassium iodide, 2 grams; distilled water, 100 c.c.).

5. The alcohol used for decolorizing should not be weaker than 95 per cent. to absolute and should not be allowed to act for too long a time, as Gram-positive organisms resist its action only for a reasonable period and exposure of the film to alcohol for longer than two or three minutes will give confusing results.¹

¹ M. W. Lyon (Jour. Am. Med. Assn., October 9, 1920, No. 15, lxxv, 1017) has recently advocated the use of acetone as a decolorizing agent for the Gram stain, applying it instead of alcohol for five to ten seconds. Some experience with the method would seem to bear out the claims made for it.

6. The counterstain must be in watery solution, must not be too strong nor allowed to act for too long a time, as it may, in such case, replace the gentian-violet and give false Gram-negative pictures.

A satisfactory technic follows. As a preliminary it is well at frequent and definite intervals, to test the stain and the technic with a known Gram-positive organism, such as the *Staphylococcus aureus* and a known Gram-negative organism, such as *Bacillus coli*, both of which are readily obtained.

Technic for Gram-staining. 1. Fix the dried film by passage through the flame, testing the degree of heat on the hand.

2. Cover with gentian-violet solution for one minute.

3. Wash off the gentian-violet solution with Gram's iodine solution (amended formula) and replace with another fresh portion of iodine solution, which is allowed to act for one minute.

4. Wash off the iodine solution with alcohol (95 per cent. to absolute), not with water, and flood the film with alcohol, tilting the slide to allow the alcohol to flow back and forth until no more violet color is given off. The action of the alcohol should not be prolonged for more than two or three minutes, which will be sufficient if the film is of the proper thickness.

5. Counterstain thirty seconds with a weak, watery solution of Bismarck brown, eosin (0.5 per cent.) or a very dilute solution of carbol-fuchsin (two drops to a test-tube full of water).

6. Wash in water, blot and mount.

It must be remembered, in the interpretation of the stained smear, that the fact that an organism is Gram-negative, and intracellular does not, therefore, determine it as a gonococcus; familiarity with the variations in its morphology are essential. As in all other laboratory examinations, in the final analysis the value of the procedure is in direct proportion to the degree with which it is correlated with the clinical findings; in a word, it is the interpretation which counts.

Summing up: For the identification of the gonococcus in the stained smear, the following conditions must be fulfilled: (a) The smear must be properly and intelligently taken and must not be too thick; (b) the staining technic must be properly controlled; (c) the observer must be familiar with the microscopic appearance of the gonococcus and allied organisms and thoroughly capable of interpreting what he sees in terms of its relations to the patient.

These premises being fulfilled and the findings correlated with the clinical evidence the bacteriologic diagnosis of acute gonorrheal infections may be made with a fair degree of certitude.

In the comparatively infrequent cases of gonococcus bacteremia cultures are required, the preparation and study of which require a trained bacteriologist, so that they are merely mentioned here.

Bacteriologic Diagnosis of Chronic Infections. It is in cases of this group—those in which the history of a previous acute attack is not infrequently wanting and in which the clinical evidence is not

always sufficiently clear to permit of a definite diagnosis—that the laboratory is most frequently called upon to make a decision.

Here, also, we may place those individuals who, admitting a previous infection, but being without symptoms, are desirous of obtaining evidence as to their freedom from foci which might prove a source of infection to others.

We may adopt any or all of three procedures: (a) Microscopic examination of stained films from selected areas; (b) the production of an acute discharge in which gonococci may be found or the production of an acute, focal reaction; or (c) the use of the gonococcus complement-fixation test.

The efficacy of the first of these depends entirely upon the locality from which and the method by which the film is taken, for, in the majority of cases, the success or failure of the examination as to decisiveness will stand or fall upon the character of the film examined.

It is necessary to keep in mind the lurking places of the gonococcus and to remember that it may be present in these places without the coincident presence of any discharge. In the male these localities are: (a) The follicles of the urethra; (b) Cowper's glands opening into the bulbous portion of the urethra; (c) the prostate; (d) the seminal vesicles; (e) rarely in the bladder.

It is necessary, therefore, for films to be made and examined from the following: (1) Material expressed by milking the urethra; (2) material obtained by the introduction of a sterile swab into the urethra; (3) from the material obtained by prostatic massage; and (4) from the centrifugalized sediment of an ounce or so of urine passed at the time of the examination.

In the female the gonococcus may persist in: (1) The urethra and the urethral ducts; (2) Bartholin's glands; (3) the cervix; (4) the uterus and Fallopian tubes.

Smears must therefore be made from material secured by milking the urethra or the introduction of a sterile swab, from material expressed from Bartholin's glands, secretion from the cervix, or, rarely, from the uterine cavity.

It must be remembered that even these procedures may fail, for the gonococcus may still be present in other localities than those examined, as in the Fallopian tubes, or, when present, may be buried in the deeper cell layers and not liberated at the time of examination. Under these circumstances an attempt may be made to produce a focal reaction by the administration of gonococcus vaccine, which may be manifested by the production of an acute discharge containing the gonococcus or by pain and tenderness in areas of metastatic gonococcal infection. Acute discharges may be produced by the use of irritants, such as silver nitrate solution.

Several observers, notably Irons,² Bruck,³ and Reiter,⁴ have

² Jour. Infect. Dis., 1908, v, 279.

³ Deutsch. med. Wchnschr., 1909, xxxii, 470.

⁴ Ztschr. f. Geburtsh. u. Kinderh., 1911, lviij, 571.

reported upon the occurrence of focal reactions following the use of vaccines, but there is an element of danger in the procedure in that a latent infection may be converted into an acute one not readily controlled.

It may be noted in passing that Irons⁵ has reported upon the production of cutaneous reactions, similar to those obtained in the von Pirquet test, occurring with gonococcal extracts; but as the cutaneous sensibility of various individuals seems to vary, and, indeed, the same individual may show extreme variations—possibly due to varying amounts of bacterial protein in the extracts used—the test is limited in value and not generally used.

The Gonococcus Complement-fixation Test. Depending, as does the Wassermann, upon the absorption or fixation of complement, the gonococcus complement-fixation test differs from it in being a true biologic reaction in that the antigen is a true antigen composed of suspensions or extracts of the causative organism.

Müller and Oppenheim⁶ were the first to report the occurrence of the reaction, further reports later emanating from Bruck⁷ and Meakins,⁸ who published the first American report in 1907. The work of Teague and Torrey,⁹ Torrey,¹⁰ Wollstein,¹¹ Watabiki,¹² Harrison,¹³ Ower,¹⁴ and particularly that of Schwartz and Schwartz and McNeill,^{15 16 17} was largely instrumental in placing the test on a practical basis, and numerous reports have now been made upon its specificity and value in determining absolute cure.

Particular advantages of this method of testing for the presence of gonococcal infection are the fact that the specimen is easily taken and the patient is not thereby informed as to the nature of the examination.

It is not, however, as widely used as it ought to be, because, owing to the small amount of antibody produced by a localized gonococcal infection, the reaction is generally weak and may often be lacking, and the performance of the test requires the highest skill and the closest attention to details, especially as concerned with the preparation and standardization of the antigen.

It is not the purpose of this review to touch upon the technic of this reaction, as it properly belongs to the domain of the serologist, with special training in this reaction; it is rather our purpose here to consider its limitations and its interpretation and the value which may be placed upon it.

⁵ Jour. Am. Med. Assn., 1912, lviii, 931.

⁶ Wien. klin. Wchnschr., 1906, xix, 894.

⁷ Deutsch. med. Wchnschr., 1906, lxx, 36.

⁸ Johns Hopkins Med. Bull., 1907, xviii, 255.

⁹ Jour. Med. Research, 1907, xvii, 223.

¹⁰ Wollstein: Jour. Exp. Med., 1907, ix, 588.

¹¹ Jour. Infect. Dis., 1910, vii, 159.

¹² Jour. Royal Army Med. Corps, London, 1914, xxii, 125.

¹³ Jour. Canadian Med. Assn., 1916, N. S., iv, 1074.

¹⁴ Schwartz and McNeill: AM. JOUR. MED. SC., 1911, cxli, 693.

¹⁵ Ibid., 1912, cliv, 815.

¹⁶ Ibid., 1910, xxii, 95.

¹⁷ Ibid., 1912, cliv, 369.

A positive reaction is of far greater value than a negative, which again emphasizes the necessity for the proper interpretation of laboratory procedures. While non-specific reactions have been reported¹⁸ the technic by which they were obtained, particularly as to the antigens used, is not stated in detail and is concomitant with the early days of the reaction, and the majority of observers are in accord in holding that a positive reaction may be looked upon as evidence of an active focus of gonococcal infection.^{19 20 21}

Factors influencing the interpretation and reliability of the reaction may be summed up as follows:

1. Because of the small amount of antibody produced, the reaction, when positive, is weaker than the Wassermann and may be indefinite.
 2. It is frequently absent in acute, uncomplicated cases,²² and may not appear earlier than six weeks after the onset.²³
 3. In acute exacerbations of a chronic urethritis the reaction is positive in about 80 per cent. of cases; in ordinary chronic urethritis with mild prostatic involvement, the reaction is positive in 30 to 40 per cent. of cases.²⁴
 4. The occurrence of an acute complication usually gives rise to a positive reaction.
 5. A positive reaction may persist for several weeks after a clinical cure, usually lasting for two or three weeks. If obtained later than that a focus of active infection is probably present.²⁵
 6. In women the reaction is positive, as a rule, only when the infection reaches the cervical canal. According to Kolmer,²⁶ in children, positive reactions occur in acute vulvovaginitis, thus evidencing that either the infection is more severe with the consequent production of more antibodies or that the cervical canal is frequently involved.
 7. The reaction is positive in about 60 per cent. of pyosalpinx cases.
 8. In cases of gonorrheal arthritis the reaction is positive in from 80 per cent. to 100 per cent.
 9. The administration of gonococcus vaccine or antigenococcic serum may give rise to a positive reaction which may persist for six to twelve weeks.
 10. The reaction has a greater positive than negative value.
- It is thus seen there is wide field of usefulness for this test which it is to be hoped, will come into more frequent and common use in the survey of gonococcal infections.

¹⁸ Uhle and Mackinney: *New York Med. Jour.*, 1915, cii, 737.

¹⁹ Thomas and Ivy: *Arch. Int. Med.*, 1914, xiii, 737.

²⁰ Thomas, Ivy and Beardsall: *Surg., Gynec. and Obst.*, 1914, xix, 390.

²¹ Kolmer: *Infection, Immunity and Specific Therapy*, 1915, 1st ed., 482 et seq.

²² Thomas and Ivy: *Loc. cit.*

²³ Kolmer: *Infection, Immunity and Specific Therapy*, 1915, 1st ed., 482 et seq.

²⁴ *Ibid.*

²⁵ *Ibid.*

²⁶ *Ibid.*

THE PATHOLOGY AND TREATMENT OF FRACTURES OF THE SPONGY BONES.

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LONG experience taught surgeons there is no single injury so likely to lead to long-continued or permanent disability as fracture near or through the articular ends of the bones. Now, while the mechanics of the disability are obvious, when a fracture causes such displacement that the articular surface of one bone is no longer con-

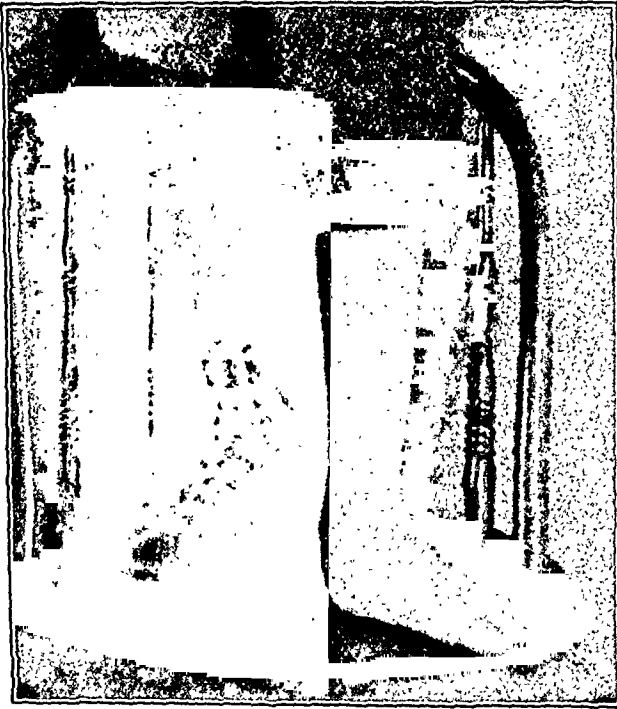


FIG. 1.—So-called traumatic flat-foot. The deformity followed an untreated injury, supposedly a sprain.

gruent with its fellow or when hemarthrosis has led to inflammation and secondary adhesions within the articulation, disability which follows these fractures, when such conditions are not evident, has not, so far as I know, been adequately explained. This pertains particularly to the fractures and injuries of the distal parts of the extremities in which the resulting disability is often quite out of proportion to the displacement, and may, indeed, be very considerable without displacement or definite signs of fractures.

The marked inflammatory reaction, the loss of motion and the tendency to valgus deformity, spoken of as traumatic flat-foot,

which follows injuries of the tarsus, is well known and particularly characteristic of this condition. This symptom-complex not infrequently follows apparently insignificant trauma, and as no fracture can be demonstrated, the condition is usually treated as a sprain, which no doubt has led to the prevalence of the belief that sprains of the ankle are more likely to lead to prolonged or permanent disability than fractures elsewhere. Following more violent trauma, with or without fracture, the distortion of the tarsal bones is often



FIG. 2.—Static deformity due to osteoarthritis of the tarsus following severe injury.

extreme and sometimes reproduces the mechanical result of weight-bearing as it would affect the bones were they made of plastic material (Figs. 1 and 2). In the carpal bones, there being no weight-bearing, marked distortion rarely occurs. On the other hand the signs of joint irritation (effusion and spasm, etc.) are equally as common and as characteristic after blows and falls upon the hands and wrists as they are of the foot. Moreover, as detail in the radiograph is more readily obtained, the decalcification and bone absorp-

tion which are the outstanding features of injuries of both carpus and tarsus are more clearly demonstrated. Thus upon examination of the radiographs of the carpal bones a week or more after their injury, especially in the cases without evident fracture or when there is only a fissure without displacement, one is struck by the close resemblance which these pictures bear to those obtained in the inflammatory or infective conditions. In many of the cases all the bones of the carpus, and in not a few some or all of the epiphyseal ends of the phalanges, show the same loss of density which is characteristic of the acute inflammatory conditions of the hand known as acute inflammatory atrophy.



FIG. 3.—So-called Kummel spine. Traumatic osteoarthritis of the spine following impact of a heavy coil of wire. Unrecognized, though the patient complained, until the deformity became noticeable.

A similar condition occurs in the bones of the vertebræ (first definitely described by Kummel and known as Kummel's spine) as a result of blows and falls upon the back. In many of these cases fracture or grave injury of the spine is not suspected until some time after the injury, when the bodies of the vertebræ apparently become softened, a kyphosis develops and symptoms of spondylitis with or without radicular irritation appear (Fig. 3). In some cases fracture of the bodies of one or more vertebræ can be demonstrated, but no

fracture is demonstrable in a considerable number of cases. Practically always the radiograph shows, besides the loss of density, deformation and the definite signs of spondylitis, a spondylitis which cannot be distinguished from that of a non-tuberculous, acute or chronic infective process.

It is not, however, only in the close resemblance of the early radiographic picture that the close analogy between traumatic and non-traumatic inflammatory conditions of the spongy bones manifests itself. Consecutive radiographic examinations of the bodies of the vertebræ, the tarsus and the carpus demonstrate that the radiographic findings after injuries of these bones resemble those due to inflammations and infections not only in the early stages, but in the advanced and terminal stages as well; so much so that in the terminal stages it is almost impossible to distinguish the decalcification, absorption, distortion, lipping, etc., of an arthritis of the spine, the carpus or tarsus, from the conditions due to trauma in those regions.

Nor is the close resemblance between trauma and infection in these bones confined to the radiographic findings. Intra-, peri- and para-articular effusion causing distention of the capsule, compression of the muscles, tendons, nerve fibers and end-organs in the neighborhood of the joint, becoming manifest by swelling, pain, muscular spasm, muscular atrophy and limitation of motion, are equally characteristic of traumatic as they are of non-traumatic conditions. Indeed, so close is the similarity of the two conditions clinically that without a history or a radiograph which actually demonstrates the presence of fracture they cannot be distinguished from each other.

Moreover, though the condition under discussion, which for the sake of brevity may be designated traumatic osteoarthritis, is more readily illustrated as it affects the carpus, the tarsus and the bodies of the vertebræ, it is not characteristic of these bones alone. It occurs in all spongy bones not only in those wholly so constituted, but also in the epiphyseal ends of the long bones which resemble them in structure. These morbid conditions with their attendant arthritic phenomena, as they occur in the shoulder and elbow, are well known. Indeed, the long-delayed recovery and great danger of permanent ankylosis which follow injuries to the elbow are almost classical examples of the condition. The fact that similar changes occur in the hip and knee, however, has not been sufficiently appreciated by the practitioner. That the conditions here are not only analogous to those which occur in the shoulder and elbow, but also analogous to those which occur in the spongy bones generally, seems to have been disregarded or entirely overlooked by all investigators. Yet the similarity of the clinical condition and the radiographic findings in the hip and shoulder and in the elbow and knee to each other and to the conditions in the spongy bones generally is so striking that the analogy between them immediately becomes apparent once the attention is directed thereto.

Thus we have a train of clinical phenomena, which follows trauma near the hip-joint so similar to those characteristic of osteoarthritic conditions that it is quite impossible, without a knowledge of the antecedent trauma, to differentiate one from the other. And this similarity is not confined to the clinical phenomena. The radiographic findings, namely, decalcification, absorption and deformation, with or without hypertrophic changes, are equally characteristic of both traumatic and non-traumatic conditions. In the knee the symptom-complex resulting from injury, as it affects the bones and the soft parts, bears the same striking resemblance to the arthritic conditions.

Evidently then the epiphyseal ends of the long bones and the spongy bones undergo similar pathological changes when subjected to trauma. Obviously this similarity is due to the similarity of the anatomical structure. Hence it may be stated that trauma to the cancellous bones, even when it is not sufficiently great to produce fracture, is likely to induce softening and absorption of the bone trabeculae, which sometimes appears soon but may not appear until some time after the injury. This pathologic condition under the stress of mechanical factors leads to distortion of the affected bones; it is accompanied by peri- and intra-articular inflammation, and as far as the symptoms and the radiographic findings are concerned, it is apparently analogous to non-traumatic osteoarthritides due to infections or other as yet unknown causes.

In order to demonstrate the pathogenesis of these morbid conditions the following experimental work was undertaken: Six dogs and six adult rabbits were traumatized over the thoracic spine with the steel bar, 6 x 1 x $\frac{1}{8}$ inches. In eleven rabbits I tried to produce fracture in the lower femoral epiphysis by indirect violence. Six dogs and six rabbits were traumatized over the great trochanter and the same number and kind of animals over the os calcis with the steel bar. It was found impossible to regulate the trauma over the spine so that actual injury to the bones without fracture could be induced. The injury was either so severe as to induce fracture of the spinous process or lamina or not severe enough to produce actual bone changes.

It was also found difficult to produce fracture near the lower femoral epiphysis without at the same time injuring the knee, but in 6 of the 11 cases I was successful in accomplishing the desired effect. The knee-joint was examined after five days in 2 cases, after nine days in 2 and after eighteen days in the remaining 2 cases. The signs of intra-, peri- and para-articular inflammation were present in all cases examined. There was an exudate which distended the tissues for some distance from the seat of injury, and this exudate was in every way similar to that found in experimental infections. The remarkably early signs of decalcification exactly similar to those which occur in the experimental infections were also found. The affected area was much softer than the normal dog bone and

at times offered very little resistance to the knife. In only one case was there intra-articular extravasation of blood.

Upon microscopic examination, from three to ten days after the injury, the subchondral region adjacent to the site of injury was found to be greatly congested. The bloodvessels were dilated, filled with blood or thrombi and the marrow spaces more or less completely filled with proliferating marrow cells. Later the trabeculae



FIG. 4.—Traumatic spondylitis. Soldier was hit by a train and treated for sprain of the back for four months. The symptoms were relieved upon the application of a back brace.

make way for the proliferating marrow cells; they apparently become first decalcified and then absorbed, leaving considerable areas within the epiphysis devoid of bony tissue. In two cases the inflammatory reaction involved the articular cartilage. In one the new-formed bloodvessels not only encroached upon but actually penetrated the cartilage, and the joint surface was covered with new-formed evidently proliferating connective tissue (Fig. 5).

In all the rabbits traumatized by a blow with the bar already

mentioned, fracture of the neck of the femur and the os calcis was induced. In dogs with similar injuries no fracture could be demonstrated in the os calcis, but in two cases fracture of the neck of the femur could be demonstrated. In all these animals the changes, namely, marrow hyperplasia, decalcification and absorption, could be demonstrated upon microscopic examinations. In these and in the animals with demonstrable fracture the conditions found were exactly similar to those in the knee-joint and the morbid



FIG. 5.—Traumatic osteoarthritis. Section from the articular surface of the femur, showing the rarefaction (the medullary cells have dropped out of some of the spaces) and a vessel penetrating the joint cartilage. The joint surface is covered with connective tissue.

process differs in no particular (except in the demonstration of the infecting agent) from that which occurs in experimental and accidental infections.

The experimental evidence, therefore, bears out the deductions drawn from the clinical findings; they must lead one to conclude that trauma with and without fracture to the spongy bone, which includes the epiphyseal ends of the long bones, induces inflammatory changes which bear a close resemblance to the non-suppurative infective processes in these structures, and like them leads to bone softening and absorption, which renders them liable to distortion when

subjected to weight-bearing. Like the inflammation due to infection, moreover, the traumatic inflammation is accompanied by intra-, peri- and para-articular exudation and the anatomic changes which are likely to induce chronic or permanent arthritic abnormalities.

The morbid process is due to the trauma acting upon the bone substance and is not secondary to the break in the bone or displacement of the fragments. It is true, of course, that the presence of the fracture indicates a maximal injury, and to a certain extent introduces a complication; the differences in the morbid process, however, when fracture is present and when it is not, are quantitative and not qualitative, the fundamental features remaining the same.

It is not possible to indicate in detail the relations which the facts here elucidated bear to the treatment of these conditions at the present time. Only a few points of general importance can be discussed. As they present the same pathological and mechanical phenomena the traumatic conditions of the spongy bones necessarily present the same problems in regard to the treatment as the non-traumatic arthritides in addition to the problem of reducing and maintaining the fragments in apposition when fracture is present.

Joint motion may be lost or restricted for three reasons: because the displaced fragments produce a mechanical obstruction; because the inflammatory reaction has led to cicatricial contraction, shortening of the tendons and soft parts; or because the decalcification and absorption of the bone trabeculae, under the stress of mechanical conditions, has led to distortion, and, as a consequence, the joint surfaces are no longer congruent. One or more of these factors may be active in a given case. The fracture and displacement only concern us insofar as their presence complicates the problem of preventing joint ankylosis or the restoration of function. This complication, however, is not nearly as great as is generally supposed. Contrary to the more or less generally accepted opinion very early mobilization is not necessary to preserve the mobility in these cases. On the contrary the inflammatory reaction in or near the joint is alleviated by rest and the fixation required to maintain fragments in apposition is beneficial rather than harmful. It is after the fracture has begun to consolidate, which is approximately the time when the inflammatory reaction has subsided, and only then that mobilization and frequent change of position is likely to promote the early restoration of function. Early and particularly indiscriminate mobilization, far from hastening recovery, in many cases actually retards it. Of this fact I have, as have others, convinced myself many times, in the treatment of fractures and traumas near the elbow. I have found, when I attempted early mobilization, that in not a few cases the elbow which permitted some degrees of motion when mobilization was instituted soon became stiff if I were too insistent. Rest, then, restored the original conditions. I found, then, that it was necessary to judge accurately how soon and to what extent the elbow could be mobilized in a given case in order to

secure the greatest benefit. The same principle holds good as regards the shoulder and wrist.

With some insignificant variations nearly all surgeons now treat fractures of the shoulder in the abducted position. Because of this fact the long and painful after-treatment, which was formerly inevitable in order to restore abduction, is now no longer necessary. But many patients are still subjected to overtreatment and are therefore compelled to endure an unnecessarily prolonged convalescence.

However, though premature mobilization is harmful, fixation cannot be unduly prolonged without predisposing the patient to long-continued or permanent ankylosis. It is plain, then, that it requires judgment, which is only acquired by constant observation and many tentative trials, to determine when and to what extent the joint should be mobilized in these cases. The conditions here are exactly similar to those in the non-traumatic osteoarthritides. In these, too, the injudicious attempts at mobilization often do harm and the auspicious moment when it may begin must be carefully estimated. Often the patient is the best judge of his condition. But this is not always true. There are patients who are too energetic as well as those who are hypersensitive and timid; and it is better to be guided by objective conditions, the relaxation of muscular spasm and the subsidence of swelling, etc., rather than, as has been suggested by a very good authority, upon the subjectivity of the patient.

I am still uncertain as to the utility of massage as an aid in hastening the absorption of the intra- and para-articular exudate. I am certain that it has no influence upon the joint effusion; on the contrary, my experience leads me to believe that even effleurage sometimes causes discomfort in the early stages. That it has any influence upon the exudate in the dense peri- and para-articular structures seems at best problematical. Superheated air, on the other hand, has some value in the treatment of traumatic as well as non-traumatic arthritis. It does not, as many suppose, exert a specific action upon the pathological process; but it does abate the hyper-esthesia and muscular spasm, and in this way forwards passive motion.

In the upper extremity the restoration of the complicated and highly specialized movements is the objective point of the treatment. As weight-bearing is an unusual function the restoration of the bone density need not be considered at all, or its consideration may be deferred. In the lower extremity, however, weight-bearing is a function equally or more important than complete joint motion. The maintenance of the morphologic structure in conformity with the mechanical conditions it must serve and the restoration of the normal bone density at the earliest possible moment are the ends to be sought.

The restoration of joint motion is, of course, to be given con-

sideration. In some cases, however, it is of secondary importance and in others it must be ignored entirely. Thus, as firm union with the maintenance of the normal angle with the shaft is much more important in fractures of the neck of the femur than the motion of the hip-joint, and as good union in this situation is difficult to obtain the future motility of the hip-joint must be ignored and all our energies directed to the treatment of the abnormal bone and mechanical conditions. Hence, as the irritation of weight-bearing with the fragments in alignment is, as far as we know, the only means by which the atrophy of the traumatized and fractured spongy bone can be avoided or the normal density restored, and as this can only be secured by reducing the fracture and maintaining the fragments in apposition by a perfect immobilizing dressing, it is clear that complete immobilization of the femur in the abducted position with actual weight-bearing is the method to be chosen in the treatment of fractures of the neck of the femur. The motion of the hip, which, for reasons which cannot be discussed at the present time, is rarely greatly interfered with in these cases, can and should be completely ignored.

That measures to prevent the distortion of the vertebræ and the resultant deformity are all important in the traumas and fractures of the vertebræ is obvious. When there are no definite signs of fracture these cases nearly always remain untreated until the deformity is evident, when it is, in the majority of cases, impossible to correct. As has been shown the decalcification and bone absorption which follow trauma of the spongy bones, and this seems especially true of the bodies of the vertebræ, often comes on gradually and not until some time after the trauma. For this reason, when there is no fracture, the symptoms and the roentgen-ray changes are often negative immediately or shortly after the accident. It is necessary, therefore, to watch all cases of severe trauma to the back carefully, or, better still, to treat them by rest in bed or immobilization even when the objective signs are negative during the period immediately after the injury. It is necessary, moreover, to continue the immobilization for a rather long time, *i. e.*, for months in the cases with positive findings if recurrence of the symptoms and chronic spondylitis are to be avoided. In the serious cases the immobilization with plaster or a back brace must be continuous; in the milder ones the patient may, without danger, be permitted to remove the brace while he is recumbent.

The treatment of the injuries near the knee- and ankle-joints is somewhat more complicated than those of the hip and spine, for in these situations it is important to secure motility as well as normal density and morphologic conformity. Unfortunately the tendency to ankylosis is much greater in the knee than it is in the hip and spine, which, particularly as regards the knee, often makes it difficult to bring the treatment to an early and successful conclusion. None the less the principles involved in the treatment of the other joints

still hold true; and though it is often difficult to determine when joint motion should begin and to what extent it should be forced, patience and good judgment will often lead to a successful result even in the apparently hopeless cases. Nor is the danger of ankylosis as a result of immobilization any greater here than in any other joints; indeed, the long-continued inactivity to which these patients are usually subjected in order to avoid immobilization is often the cause of greater delay in the restoration of function than would have been the case had immobilization been employed from the beginning. As the various parts, bones, muscles, ligaments, etc., coördinate to perform the function of weight-bearing and locomotion, and as the performance of these functions increases their efficiency, it is evident that the efficiency when lost can only be restored by actual use. The treatment, therefore, which permits of early locomotion and weight-bearing obviously will attain results much more expeditiously than that which requires recumbency. Under these circumstances a splint or dressing which holds the fragments in apposition, and at the same time permits gradually increased weight-bearing, though it necessitates the immobilization of one or more joints, is evidently the method of choice. It is because the danger of muscular atrophy from disuse is supposed to be greatly increased by complete immobilization that the fixation ambulant treatment has been discouraged and long-continued recumbency and complicated mechanotherapeutic measures substituted. It should be understood that actual voluntary movement is the only means of combating muscular atrophy. All the muscles of the limbs are coördinate in action; not one or a few muscles, but practically all the muscles contract (reflexly) when the limb is used in locomotion even when the limb is placed in an immobilizing splint or dressing. For this reason a retention splint or dressing which permits early locomotion not only promotes the restoration of the bone density and allays the inflammatory reaction, but far from inducing muscular atrophy, actually prevents it or forwards the return to normal function.

All things considered, then, provided the fracture is reduced and the fragments held in apposition, immobilization with early locomotion is the treatment which promises the earliest and surest results in the fractures near the joints of the lower extremity. Not only the physiologic and pathologic principles underlying these conditions, which are certainly conclusive, but the experience of many years of practice, with a great preponderance of difficult cases, has forced me to this conclusion.

Another word regarding the fractures and injuries of the tarsus must be added. These closely resemble the traumatic conditions of the spine; that is, the tendency to arthritis and distortion sometimes continues for a considerable time after the injury. These require, therefore, long-continued supervision, and in the majority of the cases a support, preferably a modification of the Whitman plate, which prevents valgus, should be worn for many months.

REVIEWS

THE AMERICAN RED CROSS IN THE GREAT WAR. By HENRY P. DAVISON, Chairman War Council, American Red Cross. Pp. 302; 8 illustrations. New York: The Macmillan Company.

SETTING forth "the scope, character and effect of the work of the American Red Cross during the Great War," the author gives a vivid account of early appeals for support and subsequent relief work in the Allied Armies and in every country of Europe, beginning in 1914 and carrying on after the armistice. Circumstances leading to America's entry into the war and other important events are described in connection with the varied activities of the Red Cross, making the book interesting and valuable as a historical work. The magnitude of the work done by the Red Cross cannot be appreciated through familiarity with only a few of its phases. Mr. Davison, in a very readable narrative, has assembled the facts about welfare work among soldiers and their families, sanitation, care of wounded, relief for non-combatants in stricken countries, communication with prisoners held by the enemy, economic reconstitution, care of children left destitute by the war and other activities in many lands, including Russia and the Near East, besides America and Western Europe. He pays a tribute to the loyalty of all Red Cross workers both at home and in the field, and concludes with an appeal for continued relief activities through the League of Red Cross Societies.

T. G. M.

ESSENTIALS OF TROPICAL MEDICINE. By WALTER E. MASTERS, M.D., Medical Officer, Gold Coast, Africa. Pp. 702; 250 illustrations. New York: William Wood & Co.

THIS work is a *vade mecum* for the practitioner and laboratory worker. It contains no new information and does not claim to do so, being rather a digest of present-day knowledge in this field. But in addition to this, it is an expanded note-book in which an experienced and accurate worker has noted down a host of helpful observations.

This book, then, is not for the student who wishes to read up a subject but for the worker who looks up a particular point. To

this end the good index is an important feature. Displayed headings and exaggerated paragraphing enable one to find specific information quickly, but do not make smooth reading. Under each disease the writer summarizes etiology; pathology, symptomatology, diagnosis, prognosis and treatment.

The first section treats of diseases due to protozoa. The most striking feature is a very careful and useful differentiation of the two important amebæ, the various malarial organisms and of kala-azar from oriental sore. Bacillary and helminthic diseases follow, the latter especially well illustrated.

The fourth section is on diseases of uncertain etiology and the next on venoms and poisons, with a great deal of information about snakes. Short sections on the skin and eye are followed by a valuable chapter on tropical hygiene, discussing particularly the question of water supply.

The text concludes with many useful laboratory hints.

The book is of convenient size, well printed and illustrated—the illustrations not original.

M. McP.

THE FORM AND FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM.

By FREDERICK TILNEY, M.D., and HENRY ALSOP RILEY, M.D.
Pp. 944. New York: Paul B. Hoeber, 1921.

THIS is the most important contribution to neurologic literature in years. It is essentially an anatomic work, with a morphologic approach and clinical interpretation. The fundamental concept of the authors is expressed in the second paragraph of the introduction: "The work is designed to fill the gap between morphology and the practical requirements of clinical medicine. It aims to visualize the living nervous system, to make accessible an appreciation of its vital relations to the functions which go to make up life as well as the defects in these relations which result in disease."

It is difficult to adequately review such a large book as this.

Perhaps no American neurologist has had a better preparation for such work than Dr. Tilney, who in the early part of his career devoted most of his time to anatomic research. The fruits of his labors are well known in anatomic literature. It was quite natural, therefore, for him to approach a neurologic problem from the developmental viewpoint. The book is full of original work.

In the opening part there is a general discussion of the conceptions of the nervous system and then the embryologic development is discussed, with uniform excellence. From here the book is devoted to special parts of the nervous system. For example, to the medulla oblongata six chapters are given; to the pons, three, five to the cerebellum and so on, depending upon the importance of the structure. The manner of treatment is equally thorough in each. In the

medulla the encephalization is first discussed; then relations, surface appearance and anatomy; internal structure, histology and finally functional significance and the principal syndromes. This is typical of the treatment of all parts of the nervous system.

The clinical discussion is not by any means the outstanding feature, for the book is essentially anatomical. The method of handling all clinical material is original in the sense that case histories are employed in which in each the clinical history is given and then the anatomic interpretation; the clinical symptoms being illustrated by charts and the pathologic lesion by a photograph of the part, with the location of the lesion standing out prominently, leaving no doubt in the reader's mind as to its localization.

The illustrations are uniformly excellent, there being altogether 591, most of which are original. So far as the subject-matter is concerned it is the best presentation of the anatomy and function of the nervous system in the English language. It is a credit to the authors and to American neurology.

ELECTRICAL TREATMENT. By WILFRED HARRIS, M.D. Pp. 343.
New York: William Wood & Co.

THIS is the third edition of this well-known book. A review of the former edition has appeared in this journal. It differs from the former in the fact that the discussion of radium therapy and roentgen-ray treatment have been omitted because both of these have become specialties in themselves. Otherwise, with the exception of a few minor alterations and additions, the book remains what it has been—an excellent manual on the uses of electric apparatus.

REPPRESSED EMOTIONS. By ISADOR H. CORIAT, M.D. Pp. 213.
New York: Brentano, 1920.

THIS book was evidently written for the lay public and is one of a series of similar books on psychanalysis. While its title is *Repressed Emotions*, it is really an explanation of the principles of psychanalysis. The chapter on repressed emotions in literature is interesting, particularly the discussion of some of the Russian literature and the rather extensive reference to Goncharoff "Oblomoff."

To the psychanalyst this book presents nothing new and to the neurologist it has certain information which can be better obtained elsewhere. To the layman it will undoubtedly be interesting reading, but the reviewer questions the advisability of putting such

a book in the hands of the public, whose interest in sexual literature is morbid. The only excuse for such books is one of propaganda, and in this respect it puts itself on the level of the chiropractor and osteopath. There have been too many books on psychanalysis for the "benefit" of the public in recent years. It seems to be the fashion for psychanalysts and psychologists to write upon psych-analytic subjects.

THE INTERNAL SECRETIONS AND THE NERVOUS SYSTEM. By DR. M. LAIGNEL-LAVASTINE, Paris. Pp. 57. New York and Washington: Nervous and Mental Disease Publishing Company.

THE study of the internal secretions has, in recent years, occupied increasing attention, until now practically every specialty has its own glandular symptomatology and therapeutics. It has been well said that everyone has his own proper physiology and pathology, and that the life of every individual is dominated largely, if not wholly, by his ductless gland chain. To have an adequate knowledge, however, of the function of the ductless glands, one must first of all know the anatomy, especially the physiology, of the vegetative system. The present book concerns itself entirely with the pathology of the internal secretions as they are related to the nervous system.

The author was a pioneer in this field, and this is the only essay on the subject. Consequently the English translation, which is well done, is an important contribution to neurological literature. It is by no means exhaustive and gives merely outlines for study. Perhaps one reason that the subject is not more fully discussed is because the study of the internal secretions is only in its infancy. In the plan of the book there is (1) a general discussion of the vegetative system and the relation of all the generative organs to the nervous system, (2) then there is a discussion of the different glands and the particular diseases related and the disturbances of each, and (3) the diseases and their endocrine symptoms. No neurologist can afford to be without this volume.

HYGIENE OF COMMUNICABLE DISEASES. By FRANCIS M. MUNSON, Lt., M.C., U.S.N., Ret.; Lecturer on Hygiene and Instructor in Military Surgery, School of Medicine, Georgetown University, etc. Pp. 793; 36 illustrations. New York: Paul B. Hoeber.

THE book is divided into two parts. Part I is divided into twenty chapters, deals with epidemiology, prophylaxis and sanitation.

The subjects are completely covered. For example, there are separate chapters on military, naval, railway, municipal, rural, school, prison and industrial sanitation. In addition, in another chapter on exotic hygiene and sanitation, the problems of arctic and tropical sanitation are enumerated. Other chapters that should be mentioned are those on general prophylaxis, infection and immunity, disinfection and disinfectants, insecticides, personal hygiene, hospitals, isolation and quarantine, and especially the interesting consideration of sanitary measures following great disasters.

In Part II the author discusses the separate diseases, first dividing them into classes depending on whether they are fecal-borne, insect-borne, spread by infected animal foods or spread by oral and nasal discharges. Venereal diseases and wound infections each occupy separate chapters.

The illustrations are instructive and helpful. The book presents in concise and readily accessible form the latest facts about the epidemiology of the communicable diseases "ashore and afloat" and their management.

A. G. M.

WITH THE DOUGHBOY IN FRANCE. By EDWARD HUNGERFORD.
Pp. 291; 8 illustrations. New York: Macmillan Company.

FROM the front-line trenches to the base ports, in hospital, camp and leave area, the doughboy was always able to turn to the American Red Cross for food, shelter, help or pleasure. And how this was made possible, and carried out, and how, also, the French soldier and civilian were taken care of at the same time, is all pictured for us in this very readable book by Mr. Hungerford.

P. F. W.

HYGIENE, DENTAL AND GENERAL. By CLAIR ELSMERE TURNER, Assistant Professor of Biology and Public Health in the Massachusetts Institute of Technology; Assistant Professor of Hygiene in the Tufts College Medical and Dental Schools. Pp. 400; 52 illustrations. St. Louis: C. V. Mosby Company.

THIS book is an up-to-date presentation in concise form of the fundamental principles of hygiene, prepared primarily as a textbook for dental students in conformity with the present-day tendency toward education of the dental student on broader medical lines. Its usefulness, however, should by no means be limited to the dentist, for it contains a mass of valuable information for the student of medicine and of public health. Two chapters alone, comprising thirty-seven pages, concern themselves with the

special hygiene of the mouth and oral prophylaxis. The remainder takes up such subjects as diet and dietary diseases, physical exercise, heredity, disease prevention, immunity, communicable diseases, public health administration, school hygiene, ventilation, heating and lighting. Every dental school should give a course in hygiene, and there is no book at present published giving the essentials of a course so suitably as the volume under discussion. R. H. I.

INFECTIOUS DISEASES. By CLAUDE BUCHANAN KER, Medical Superintendent City Hospital, Edinburgh. Second edition. Pp. 627; 32 plates and 68 charts. London: Henry Frowde, Hodder & Stoughton.

THE introductory chapter of this standard and practical textbook is of great interest and only too short. Here various factors related to infectious and contagious diseases are dealt with in abstract. Bacteriology, infection, the incubation period, toxins, immunity, anaphylaxis, fever, the symptoms of fever, the stage of fever, management and treatment of fever, serum and vaccine treatment, diet in fever, diagnosis of eruptions and prophylaxis are the subjects considered. A decidedly fair and impartial mind is displayed by the author. For example, the difficulties of the laboratory worker are recognized—"Even a positive report sent from a laboratory does not necessarily mean that a patient has diphtheria, but that an organism corresponding in its staining properties to the bacillus of that disease, has been successfully isolated."

The diseases considered by separate chapters are measles, rubella, scarlet fever, small-pox, vaccinia, chicken-pox, typhus fever, enteric fever, diphtheria, erysipelas, whooping-cough, mumps, cerebrospinal meningitis. There is also a chapter on fever hospital problems. The author states in the preface that the book is for the most part a record of personal experience supplemented by information gathered from the best sources. Much more than most books is this volume tinctured by personal experience. Especially in the treatment of the diseases is the author frank in telling what he has tried and what has been of value to him. He then gives the conclusions of other authorities.

Illustrations and colored plates are of distinct value in a book of this kind and in Dr. Ker's book the illustrations are many and excellent. The volume could not be otherwise than valuable to any practitioner of medicine.

A. G. M.

A SYNOPSIS OF MEDICINE. By HENRY LETHEBY TIDY, M.A., M.D., B.Ch., F.R.C.P., Assistant Physician to St. Thomas's Hospital; Physician to the Great Northern Hospital. Pp. 952. New York: William Wood & Co., 1921.

THIS book is, as its name implies, a synopsis of the various diseases that one meets in medicine. It gives the essentials of each disease reduced to an irreducible brevity. The volume is not intended for a text-book. Indeed, the author says in the preface that it is only meant for those who have to revise rapidly their knowledge of medicine in general or of some disease in particular. To the student, to the hurried practitioner or to the teacher who has but a few brief minutes to run over his lecture for the day the book will prove of value, and as it is intended for these men, it obviously fulfils the purpose for which it is prepared.

J. H. M., JR.

CUNNINGHAM'S MANUAL OF PRACTICAL ANATOMY. Revised and Edited by ARTHUR ROBINSON, Professor of Anatomy in the University of Edinburgh. Seventh edition, in three volumes. Vol. I, Superior and Inferior Extremities. Pp. 451; 203 figures. Vol. II, Thorax and Abdomen. Pp. 524; 231 figures. Vol. III, Head and Neck. Pp. 568; 233 figures. New York: William Wood & Co.

IN the present edition of this well-known manual the subject-matter is arranged in three volumes instead of in two volumes, as in the previous six editions. The rearrangement has been made necessary by the addition of over 200 pages to the work. This is a striking change, for a comparison of the first and sixth editions shows that they contain practically the same number of pages of text. However, the present increase is due not so much to increase in the printed matter as in the illustrations. At each successive edition there has been an increase in the number of these until now in the seventh edition there are twice the number which appeared in the original work. In the sixth edition 27 plates were added at the end of the volumes, showing roentgen-ray figures of bones and joints, stomach, colon, etc. In the present edition these and other additional figures have been distributed throughout the volumes, in close relation to the descriptive text. In recent years there has been quite generally a reduction in the number of hours allotted to gross anatomy in the medical school curriculum. It will be interesting to see how the change from two to three volumes will affect the popularity of this well-established manual. W. H. F. A.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Nature of Arthritis and Rheumatoid Conditions.—PEMBERTON *Jour. Am. Med. Assn.*, December 25, 1920, lxxv, 1759-1764). In this report the author offers a working hypothesis of this disease, based on recent reseaches of others and an extensive investigation carried out by him while in government service. He notes that while the importance of focal infection was abundantly illustrated in his cases (young men) still the subjects of the study showed a considerable independence of it. The important role played by exposure and wet alone suggests that focal infection is not the only etiological factor. It may, however, serve as a precipitating factor in these cases. It is noted that agents which hasten metabolism as a whole may have a decidedly beneficial effect on arthritis (x -ray, radium, thyroid extract, muscular exercise, psychic disturbances). Moreover, there is in arthritis a difficulty in the utilization of food as indicated by the therapeutic effect of lowered diet and by the frequent presence in these cases of a lowered sugar tolerance. The latter is interpreted as evidence of disturbance of some of the oxidative and combustive processes of the body. Ingestion of carbohydrate in large amounts is sometimes harmful in arthritis. Conversely, the fact that arthritis rarely occurs in diabetes is noted. The fact that rheumatoid conditions occur chiefly in joints and muscles is noted and a partial explanation is offered in that in the joints, on account of their poor blood supply, oxidative metabolism is sluggish, and in the muscles takes place an important part of the metabolism of sugar, one substance known to stand in some relation to the disease. Factors affecting oxidative function are discussed (areas of varying CO₂ tension in the circulating blood; temperature of the blood at a

given point; barometric pressure; factors making for acidosis, etc.). Once the relation of the oxidative functions of the blood to arthritis has been established, these considerations will find application. The author feels that rheumatic and arthritic phenomena find their chief explanation on these principles, and offers the following working hypothesis of the disease: There is a lowered respiratory or metabolic capacity possibly in the circulating blood. This is able to achieve a certain amount of its normal function but not all; those sites therefore at which metabolism is normally most sluggish (joints) are first to suffer. Hyperemia of a part involved often suffices to restore metabolic conditions locally, but does not necessarily relieve the general situation. Thus the disturbance may pass rapidly from one joint to another. That reduction of temperature lowers the dissociation curve of hemoglobins for oxygen is offered as a possible explanation of myositis and arthritis due to exposure. The beneficial effect of heat in arthritis may be explained by the raising of the dissociation curve together with the local hyperemia produced. The author feels that it is reasonable to believe that many factors as many types of infection, exposure to wet or cold, chronic intestinal conditions, possibly interglandular disturbances may induce the substratum, partly illustrated by a lowered sugar tolerance, which is shown to accompany this disease so closely. The paper is concluded with a discussion, along general lines, of treatment.

Failure of Antibody Formation in Leukemia.—HOWELL (*Arch. Int. Med.*, 1920, xxvi, 706) has made observations upon antibody formation in lymphatic leukemia and in myeloid leukemia with the following results: "Individuals with leukemia who contract typhoid or paratyphoid infection may fail to develop the specific agglutinins in the blood. A similar failure of agglutinin formation also occurs when a leukemic individual is injected with typhoid vaccine in a dosage which causes agglutinin formation in a normal control. Opsonins are also absent in the blood after injection with typhoid vaccine. The failure of both opsonin and agglutinin formation after typhoid vaccination, as shown in the 2 cases reported here, of agglutinin formation in Moreschi's spontaneously infected cases and in his vaccinated cases, and of agglutinin production after vaccination with still another bacterial species, as shown by Rotky, may indicate that the tissues of the leukemic individual have lost the property of antibody formation in general. The loss of ability to form antibodies is probably the result of the marked alterations in the hematopoietic tissues which characterize leukemia. This loss of ability may be due to the excessive proliferation of the hematopoietic tissues, one of whose normal functions is the formation of antibodies. With rapidly repeated cell generations the cellular energy used in multiplication prevents the utilization of the energy which is necessary for normal function. The temperature reaction after bacterial vaccination in leukemia is variable. When a rise in temperature occurs it may not be associated with antibody production. The leukocytic reaction after vaccination is also variable. Some cases react like normals with an increase in the number of circulating leukocytes. Others show no changes. In still others a decrease may occur. The variable leukocytic reaction, like the failure of antibody formation, is probably the result of the alterations in the hematopoietic tissues."

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

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TO THE UNIVERSITY HOSPITAL.

Ether; Oil Colonic Anesthesia.—LATHROP (*Jour. Am. Med. Assn.* 72, 2, 82) says he has used this form of anesthesia in 1002 surgical operations, chiefly goiter. The safety of the method is shown by several factors, such as the rate of evaporation of ether from oil, in accordance with well-known physical laws. The ether passes off slowly, especially at body temperature. When the colon is fully distended less ether is absorbed. It is important that the anesthesia be carried on by a trained person. The evening before operation an enema of soap-suds (2 pints) is given. In the morning a second enema of 1 or 2 pints of clear tepid water is given. One and a half hours before operation 2 drams of olive oil (warm) and 3 drams of paraldehyde and 4 drams of ether are given. Twenty minutes later morphin sulphate, grain $\frac{1}{4}$, and atropin sulphate, gr. $\frac{1}{150}$, are given hypodermically. Thirty minutes later 3 or 4 ounces of ether and 2 ounces of olive oil (warm) are given. The oil and ether are shaken thoroughly before introduction into the rectum. The patient should be on the left side with both knees flexed, the right acutely. A rectal or colon tube is inserted not more than six inches after all air has been excluded. The mouth and nose are covered with several thicknesses of gauze. The mixture should be given slowly, about 1 ounce a minute. The funnel attached to the tube should be held about 3 inches above the level of the patient. The tube should be clamped and allowed to remain in the rectum so as to be able to withdraw the mixture if desired. If the patient cannot retain the mixture one should not try to repeat the procedure. The patient should be ready for operation in from twenty to thirty minutes from the time of the last injection. The reversed Trendelenburg position seems to aid in maintaining an even plane of anesthesia. When the operation is completed the bowel should be irrigated with tepid water until the water returns clear. One pint is then put in the bowel and left or 4 ounces of oil may be used. The author finds the method most useful in toxic goiters and has used it extensively in these cases. The method is contraindicated in rectal diseases or when pain is caused by its introduction.

Fracture-dislocations of the Ankle.—ROULANDS (*British Med. Jour.*, December 6, 1919, p. 1575) says these serious accidents are commonly followed by bad results. It is a common mistake to regard a fracture of the lower part of the fibula without any displacement at the ankle as a Pott's fracture. In a typical Pott's fracture the fibula is broken in the lower third and either the internal malleolus is detached from the tibia or the internal lateral ligament is torn. This allows a rotation on the

inferior tibiofibular articulation. The outer edge of the superior articular surface of the astragalus becomes uppermost and is drawn backward. In a Dupuytren fracture we have the lesion already described plus a tearing of the inferior tibiofibular ligaments or a vertical fracture in the tibia just mesial to the tibiofibular articulation. The outer and upper wedge of the rotated astragalus then becomes the apex of the wedge which increases the separation of the tibia and fibula. This separation also occurs in oblique upward and outward fractures of the fibula from just below the inferior tibiofibular articulation. Rouland believes these fracture-dislocations are some of the most serious injuries of the lower limbs, since the abduction, eversion and flattening of the foot increase with time. Osteo-arthritic changes soon take place in the ankle and metatarsal joints and later the knee and hip may become affected. In all roentgen-ray examinations, and these are essential, the ankle should be examined in both the anterior posterior and the lateral position. The complete reduction is difficult and only by operation can the fragments be brought into perfect apposition. There are different views as to the necessity of getting perfect apposition. When treated conservatively an anesthetic should be given in order to properly reduce the fracture. In some cases division of the tendo Achillis is warranted. Reduction should not be attempted after swelling has appeared until it subsides. It is easier to maintain a good position with a plaster splint than by any other means. Roentgen-ray examination should be repeated. After three weeks massage and passive movements begin. No weight-bearing is allowed for eight weeks and the inner border of the boot is built up when this begins. When the above method fails to get a good reduction operation can be done within one week of the accident. The fibular fracture is wired or plated. The tibiofibular separation is corrected with a long screw. In many cases this is all that is required. The long screw has been retained by many for years. Correction of the deformity and restoration of function in late cases is difficult. The tendo Achillis must frequently be divided at operation, and this is best done by dividing the two lateral halves at two levels. The tibia is divided three-fourths of an inch above the level of the tip of the malleolus and the deformity slightly overcorrected. The after-treatment is similar to that given under conservative treatment.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Immunization against Diphtheria in a Large Child-caring Institution.—BLUM (*Am. Jour. Dis. Children*, July, 1920) made Schick tests in 1076 children in an institution during a period of five years. He found that a negative Schick test is evidence of the presence of sufficient antitoxin in the tissues to protect the individual against diphtheria infection. The

moderate or slightly positive test denotes an insufficient amount of antitoxin in the tissues to protect the individual. The tests called very faintly positive show possibly sufficient antitoxin to protect, but it is possible to transfer virulent organisms to these individuals, which may not only cause them to become carriers, but may cause them to suffer from a superficial infection without any constitutional toxemia. Tests made on 72 families showed that the younger members of the same family usually gave corresponding reactions to the Schick test. When variations did occur the younger members gave usually the positive and the older the negative reactions. Infants under six months of age because of the transmitted immunity from the mother were exceptions to the rule. Change in the Schick reaction from negative to positive during the first three years of life, due to the loss of inherited immunity, were found to be sufficiently numerous to justify retesting during this period, at intervals of a few months. The full duration of the active immunity conferred on individuals susceptible to diphtheria by the injection of toxin-antitoxin is not yet ascertained. In one series the immunity persisted in 100 per cent. of the cases of a group of 50 children for at least twenty-two months. Once acquired, immunity may last for four and a half years. The institution in which this study was conducted has been kept free from diphtheria for a period of five years.

A Study of the Malnutrition of School Children.—BROWN (*Jour. Am. Med. Assn.*, July 3, 1920) made a study of the children of a school in which 41 per cent. of the pupils were at least 10 per cent. under weight. She found that the two factors chiefly responsible for the beneficial results were the work of the school nurse in securing home coöperation and the selection of food with reference to supplying the dietary deficiencies of the home. One of the most interesting observations was that these children readily stowed away from 1000 to 1800 calories in addition to their customary three meals. The mothers reported that they ate more at home as well. This indicates that the amount of food needed by growing children has been underestimated. No correlation was found between the rate of growth of these children and any social conditions. The time of the observation was too short to show the favorable results of the other elements of the health service. If a few weeks longer had elapsed it is probable that a favorable result would have been shown by the correction of dental defects and the removal of diseased tonsils and adenoids. Two facts stood out. These children in spite of adverse conditions and handicaps were so badly in need of food that they made a gain of 278 per cent., or 302 per cent. gain over a control group. Nine and half months of intensive health service brought this school from the lowest rank in the city to third place.

Precipitins for Egg Albumen in Stools.—GRULEE (*Am. Jour. Dis. Children*, July, 1920) studied the stools of three groups of cases to ascertain the digestion of egg albumen. In the first group 103 stools from 24 cases were examined, with three positive reactions. These were all from children of two years or over. Two of the positive reactions occurred in a case of idiocy. This child took large quantities of egg in the diet while the other children in this series were only given

egg in ice-cream or puddings once or twice a week. The other positive reaction occurred in the stool of a case within forty-eight hours after taking the diet. In seventeen other stools from the same case no positive reaction occurred. In the second group a teaspoonful of egg albumen was given each day to a control case through a gastrostomy wound, to a case of intestinal infantilism and to a case of general eczema. In seventeen stools from these cases only one showed a doubtful reaction. The third group of 33 cases of infants of two years or under, furnished 221 stools. In only two of these cases was the age over one year. Many were newborn infants who had received albumen water of a strength of 10 c.c. of egg albumen to 500 c.c. of water. Five stools gave positive reactions. One of these occurred in a newborn infant. In the other three children there was no albumen in the diet. From this observation it is seen that egg albumen is nearly always completely broken down by the digestive processes of infants and children.

The Effect of Splenectomy upon Growth in the Young.—HENN (*Am. Jour. Physiol.*, July, 1920) says in this work that the results of observations on rats and rabbits are sufficient to permit of conclusions as to the effect of splenectomy upon growth. He felt that he was not justified in drawing conclusions upon the results of his two series of experiments on kittens, although their weight curves were similar to those of rats and rabbits. In dogs there were early influences of dis-temper and gastro-intestinal disturbances that presented a factor that was not ruled out in other animals. The resistance of blood corpuscles to hypotonic sodium chloride solutions was found to be true in animals operated upon while young as well as in others operated when older. *This suggests that the spleen may have the function of preparing the blood for destruction.* The quickened coagulation of the blood from splenectomized dogs may be a protective means against the loss by hemorrhage during the time of the anemia. The results suggest that the earlier that an animal is splenectomized the more rapid is the time of coagulation. It may be due to the general leukocytosis or to an increased amount of fibrinogen, which may account for the large amount of fibrin secured when the blood from splenectomized animals is defibrinated. This increase of fibrinogen may be due to a greater production by the liver in the absence of the spleen. No difference was noted in activity or temperament in rat, rabbit or dogs, but a slight difference was seen in kittens. This may be due to some individual variation rather than to any effect following removal of the spleen. In rabbits it was clear that the females were not rendered sterile. In rats neither sex was sterilized. Histological examinations suggested that the spleen was somehow connected with the blood. The presence of large hemolymph glands, especially in the mesentery, suggested that if this was a compensatory hyperplasia following splenectomy it is important that such a function should be produced in the portal circulation. The bone-marrow changes were striking. The bone-marrow through the different types of cells present indicated that there was a process of erythrogenesis and leukogenesis taking place while an increase of Kupffer cells and endothelial cells of lymph glands indicated a process of blood-destruction.

The Treatment of Indigestion in Children—MORSE (*Jour. Am. Med. Assn.*, July 10, 1920) says that there is no place for the so-called digestants in the treatment of chronic indigestion in children. There is probably never an insufficiency of hydrochloric acid or pepsin, and as pancreatin is destroyed in the stomach it can be of no use. The main essentials of treatment consist primarily in regulation of the diet to fit the digestive capacity of the individual child. Examination of the stools is of importance in controlling this factor. In the cases in which there is marked clinical evidence of fermentation, bacteria undoubtedly play an important role. In cases in which the evidence of fermentation is less they may also be an important cause of trouble. It is of the greatest importance that bacterial activity be limited. He says that it is impossible to change the intestinal bacterial flora by giving bacteria by mouth, although it may be temporarily limited by the continuous administration after this manner. The best way is by changing the composition of the food. Diminishing the proportion of the carbohydrates and increasing that of the proteins changes the flora from the fermentative to the putrefactive, and by doing the reverse the flora may be changed from the putrefactive to the fermentative. This can be shown by bacterial examination of the stools, but can be as readily shown by the reaction of the stools, as the stools are acid when the flora is mainly fermentative and alkaline when the flora is mainly putrefactive. Organisms growing on fat have relatively little to do with fermentation in the intestinal tract, but the products of their activity increase the activity of the stools. When the organisms of the gas bacillus group are the cause of the fermentation of the intestinal contents much may be done by the administration of the organisms that produce lactic acid. The best type is *Bacillus bulgaricus*, and the best results are obtained when it is given in the form of buttermilk. In addition to a greater number of bacteria the buttermilk contains considerable lactic acid. There is no place for drugs except for temporary relief.

Frozen Milk.—MIXSELL (*Arch. Ped.*, May, 1920) presents a problem about which the physician is frequently questioned, especially in our Northern States, during the winter months. Owing to the marked difference of opinion of authorities he makes it a rule to use some other feeding if the milk has become frozen. This is especially done in the case of young infants. He states that he has never seen personally any deleterious effects from the ingestion of frozen milk. It is perfectly possible that a putrefactive diarrhea may ensue, owing to the growth of the putrefying bacteria at low temperature and the breaking down of the proteids into amino-acids, or to have a diarrhea as the result of lactic and fatty acid formation. It has been shown that there is no increase in the number of bacteria in forty-eight hours. After that time the increase is marked, although the usual lactic acid forming organisms are not present in sufficient quantities to form a curd. There is rapid proteolysis which is pronounced at the end of two weeks. The acidity is markedly increased, owing to the bactericidal action on lactose changing it to lactic acid. No marked change in the fat has been noted except that caused by bacteria.

OBSTETRICS

UNDER THE CHARGE OF

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The Use and Abuse of Castor Oil.—In the *Journal of the American Medical Association*, November 29, 1919, occurs an editorial on this subject. It must be remembered that castor oil contains an irritant substance, ricinoleic acid, which is produced by the digestion of the oil in the intestine. This excites peristalsis, causing the small intestine to empty itself into the colon in two hours, instead of in the normal eight. Castor oil contains an unsaturated fat acid which is absorbed and may be assimilated and become of food value. It is an article of diet in China. The action of castor oil is somewhat independent of the dose, and the dose is not much influenced by the age of the patient. An infant may safely have a teaspoonful or two of castor oil, although this dose will usually cause a marked result in the adult. When the oil is not entirely digested the undigested portion passes through the bowel as a lubricant, acting like petrolatum. Excessive action of castor oil is practically impossible. When, therefore, there is difficulty in giving an adult person one or two tablespoonfuls it must be remembered that satisfactory results are frequently obtained with very much smaller dose. Because of its thoroughness and reliability of action the impossibility of excessive effect and usually its lack of irritation castor oil is greatly used by pregnant women. It rarely causes intestinal griping and so is a good remedy for intestinal colic. Daily doses of castor oil have often relieved obscure abdominal pain and chronic irritation of the intestine. When intestinal obstruction is suspected castor oil is probably the least objectionable of the reliable cathartics. If a liberal dose fails to act drastic purgatives should be avoided. One of the objections to the use of this substance is the fact that in most cases it leaves the bowels sluggish after it has produced an evacuation. In chronic constipation it is one of the worst drugs. Because of its soothing qualities it is often the best possible substance in cases of irritant diarrhea. Doses (teaspoonful) of it produce no irritation, and when compared with magnesium sulphate and calomel castor oil seems to have the least irritating action. A dose usually acts in from four to six hours. It has a tendency to delay function of the stomach, and is best given on an empty stomach an hour before breakfast. It is possible to so refine castor oil, if it be protected from the influence of the air, that it is almost devoid of odor and taste. Such oil should be procured in bottles, used while fresh and the bottle kept carefully corked. Elastic capsules furnish an excellent medium for the administration of castor oil, 2.5 c.c. being none too much for adult persons. These capsules may be swallowed more easily if they are dipped in water for a moment just before taking, and if the patient will look down while swallowing, as he does while eating his food, the capsule will pass down more readily. Holding the head up while attempting to take pills or capsules is a frequent cause of inability

to swallow them. Two of these capsules usually give a very good result. If a much larger amount is required it is best given in the form of the so-called sandwich. Such a sandwich is prepared by placing in a small tumbler or medicine glass a layer of thick syrup of any flavor desired. The glass is inclined in such a manner as to coat its inside almost up to the rim with the syrup. The oil is poured into the center of the glass, care being taken that it does not run down the side. Over the oil is put a layer of aromatic elixir, and while the dose is being taken the edge of the glass should be placed in the lower teeth to avoid straining the oil through the teeth, as some will adhere and occasion an unpleasant taste. A newborn infant needs no disguise for castor oil. The taste sensation in the infant is not well developed at birth. When, however, the child begins to taste the oil as it grows the oil should be disguised. If possible a day's fasting is an excellent preparation for the action of castor oil in children. Some children will take oil better if it be sweetened and if aromatics are added to it. Saccharin dissolved in alcohol will sweeten castor oil very pleasantly. Aromatics may then be added which greatly improve the taste and action. It is sometimes necessary to administer castor oil without the knowledge of the patient. If the so-called tasteless oil is shaken vigorously with four times its quantity of hot milk, and if the dose be taken immediately, it is practically tasteless or has the pleasant taste of the aromatics employed. Such oil might also be given floating on hot soup. Care must be taken not to excite a prejudice against some article of food by mixing it with castor oil. Emulsification lessens the activity of this substance, probably because in this form it is too rapidly digested and assimilated. A 35 per cent. emulsion of castor oil is palatable and can readily be made. It may be flavored with tincture of vanilla. In the observation of the reviewer a child was given castor oil mixed with the yolk of a raw egg; this created such disgust for eggs that the patient, now a grown woman, has never been able to take them. Castor oil has at present a considerable reputation in inducing labor in pregnant women. There is no objection to its use, but it will often fail utterly to accomplish its purpose. It should be given at night, disguised with fruit juices, aromatics or a small quantity of whisky or brandy. The action of the oil upon the bowel is greatly enhanced by high colonic irrigation on the following morning. For the induction of labor, quinin is frequently given with castor oil, and then it may be difficult to determine if labor begins which drug has been efficient. In pregnancy, in the puerperal state, the administration of castor oil repeatedly tends to make the bowel sluggish and hence for habitual action is not to be preferred. Compound licorice powder is agreeable to most persons and produces a better result nor does it in the pregnant person seem to lose its effect. Castor oil is employed by some as an application to the nipple of the pregnant woman to prepare the nipples for nursing. It may be combined with some substance which is astringent and castor oil and bismuth is a combination considerably used.

Premonitory Signs of Eclampsia.—VAN CAUWENVENGE (*Revue franc. de gynec. d'obst.*, August, 1919) believes that eclampsia may be imminent in a patient whose urine is apparently normal. There will, however, have been digestive disturbances in such a patient, and frequently

intractable vomiting. It may be necessary to bleed such patients, for if the woman comes into labor she should be allowed to lose a reasonable quantity of blood. Pituitary extract should be avoided in the management of these cases. In one of five recent cases of eclampsia a primipara of eighteen had no symptoms whatever except a little pain in the stomach when eclampsia developed. In one, except for two periods of vomiting, one early and one late in pregnancy, the conditions were normal, but the patient died in convulsions. Another patient had inertia of the uterus, accompanied by frequent vomiting, and was given pituitrin. The delivery was rapid, but the uterus kept contracting for forty-eight hours after labor, and there was scarcely any of the normal blood loss. Thirteen hours later cramps developed in the stomach, followed in four hours by convulsions and coma, but the woman recovered. In two previous pregnancies she had vomiting, but no eclampsia. In her last delivery the pituitary extract had locked up the uterus so that the usual loss of blood did not occur, thus producing congestion, and the accumulation of poisoned blood had produced eclampsia. Very probably the immediate factor in this result was the intense uterine contractions which the patient had. In the fifth case the patient had no albuminuria, but when labor came on there were headaches, disturbances of vision and a little edema in the feet. Expulsion was rapid and a considerable quantity of blood was lost. This persisted, but was not checked, and very soon the patient's headaches subsided and her symptoms disappeared. The writer is convinced that this hemorrhage saved her from eclampsia.

The Justo-minor Pelvis.—DANLIN (*Revue franc. d. gynec. d'obst.*, August, 1919) by this term describes a pelvis that is too narrow in a patient otherwise well formed. Sometimes the type of pelvis is adult, but unusually small, or it may be funnel-shaped, of the infantile type. The hips are narrow, the measurement from crest to crest 24 or 25 cm. instead of 28, and between the spines 18 to 21 cm. These patients menstruate late and there is some disturbance of the ductless glands, and this causes a premature junction of the points of ossification, which stops the growth of the pelvis just as the premature closing of the fontanelle stops the growth of the skull. The obstetrician can usually be warned of this condition by external measurements and by the use of the roentgen ray. Induced labor should be avoided in these patients and Cesarean section at term if the conjugate diameter is 9 cm. or less is far better. If the obstetrician attempts to deliver through the vagina the use of forceps is better than version. The head should be in the oblique diameter and a pair of forceps should be chosen which fits the head well. In this type of pelvis the difficulty increases as labor proceeds.

Prolapse of the Uterus in Pregnancy.—BERNALDEZ (*Jour. Med. Ibra.* special number, 1919) records the case of a multipara who had suffered in her first labor a complete tear of the pelvic floor which had never been closed. She had afterward two labors. In the fourth pregnancy she had complete prolapse of the uterus. The entire womb had descended through this enormous tear, but the symptom which most distressed the patient was retention of urine. The bladder could be emptied by catheter, but the lack of support of the ligaments by the

pelvic floor was such that it was impossible to reduce the uterus. As the result of the exposure and constant irritation the cervix was deeply congested and ulcerated. The question of treatment was a difficult one. It was impossible to keep the uterus in place by the use of tampons while the pregnancy continued. As the cervix was infected it was dangerous to bring on labor. If the uterus was to be entirely removed an abdominal section was inevitable and this might cause fatal peritonitis. The patient had a spontaneous abortion, but passed out of observation and her subsequent history is unknown. In a somewhat similar case the reviewer kept the patient in bed for two months before delivery, using antiseptic solutions upon the cervix and sterile dressings. In this way the infection and inflammation largely subsided and the patient passed through a spontaneous labor successfully. She was afterward subjected to operation.

GYNECOLOGY

UNDER THE CHARGE OF

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Value of Smears in Diagnosis of Gonorrhea.—When dealing with inflammatory lesions of the lower genital tract it is advantageous to determine the type of infection present, but NORRIS and MICKELBERG (*Jour. Am. Med. Assn.*, 1921, lxxvi, 164) point out that during the acute stage of the gonococcal infection the diagnosis is generally made without difficulty, as the clinical signs are more or less significant; if doubt exists, film preparations can be depended on. During the chronic stage the clinical signs are less characteristic than during the acute stage and the examination of smears is also less satisfactory. The presence of gonococci can be demonstrated by film preparations from every case if a sufficient number of correctly performed examinations are made. A single negative smear examination is without significance. In such a case the chances of demonstrating gonococci are about three or five to one according to the skill of the examiner and even under the most favorable circumstances, positive film examinations can be obtained in only a relatively small proportion of cases. Unless safeguarded by the Gram stain, smear examinations are valueless and even with Gram's stain errors in diagnosis may occur since differences in the thickness of the preparations, slight overstaining or understaining, etc., may lead to extremely misleading results. Owing to the many difficulties surrounding this form of diagnosis, the authors believe that unless the test is performed by one experienced in the

work, its results are of no value and are often actually misleading. They believe that clinical evidence is of far greater value than staining methods, even when the latter are performed by an expert and from a practical standpoint all cases should be regarded as of gonococcal origin until proved otherwise.

Management of Cervical Stump.—BISSELL (*Surg., Gynec. and Obst.*, 1920, xxxi, 578) is firmly opposed to the common practice of anchoring the round and broad ligaments to the cervical stump in the performance of supravaginal hysterectomy, on the ground that such practice displaces the stump and does not hold it in its proper position as it is supposed to do. In the follow-up clinic of the Woman's Hospital he has examined 130 cases of supravaginal hysterectomy done without anchoring the round ligaments in the cervical stump. In 127 of these cases the cervix was in normal or practically normal position prior to operation, and in not a single instance was the cervix found prolapsed after operation. In 3 cases the cervix following operation was found prolapsed with considerable relaxation of the anterior vaginal wall. In each instance, however, the conditions existed prior to operation: two of these cases were operated upon a second time, the cervix in each instance was removed and the fascia of the anterior wall lapped. The results in these cases were successful while the third case is awaiting operation. Bissell believes, therefore, that the condition of the pelvic floor is of much more importance in maintaining the cervix in its proper position than the anchorage of the stump to the ligaments, which procedure tends to displace the stump forward.

Treatment of Fibroid Tumors.—The conscientious and thoughtful operator makes every effort to preserve the menstrual function of his patient when dealing with fibroid tumors of the uterus. VINEBERG (*Med. Rec.*, 1921, xcix, 91) insists upon the importance of preservation of the menstrual function, for the ovaries, to his mind, serve no useful purpose when the uterus has been removed or when the endometrium has been destroyed, so that menstruation is no longer possible. Some of the very worst cases of the artificial menopause syndrome have been witnessed in women who had their ovaries and their uterus *in situ*, but in whom a too energetic curettage had brought about a permanent cessation of menstruation. The same applies to instances when the uterus was removed and the ovaries left behind. There is to be observed at the present time a singular state of mind on the part of the medical men. They are all keenly alive to the importance of conserving the menstrual function in women. They hesitate, to their credit, to consign their patients to an operation which would destroy that function. Still they will refer, without a moment's hesitation, a patient with a bleeding fibroid of the uterus, to the roentgenologist or radiologist, who can only be successful in destroying that function and, in most instances, permanently. Every patient who consults the writer regarding a fibroid tumor causing symptoms is told that she may have her choice of treatment, either by operation or by roentgen ray or radium. He tells her, regardless of her age, that the one (operation) perhaps carries more risk with it than do the others, but that in his opinion it is a more certain, permanent cure. If she is under forty he tries to impress her

with the advantages, of which he is strongly convinced, of submitting to an operation, the endeavor of which would be to remove her tumor or tumors and preserve her menstrual function. In spite of our strongest determination and most painstaking efforts, it must be admitted cases will now and then be encountered in which it is not possible to save the uterus. What we must endeavor to do, then, is to save enough of the organ and endometrium to carry on the function of menstruation. Even should we be baffled in this, and the entire organ have to be sacrificed, the patient would in no wise be any worse off regarding her menstrual function than she would have been had she been successfully treated with roentgen ray or radium. On the contrary, the writer believes she would be better off, for her cure would be more certain and more complete.

Action of Emmenagogue Oils on the Uterus.—Some experiments which have been performed on the isolated human uterus by GUNN (*Jour. Pharm. and Exp. Ther.*, 1921, xvi, 485) to determine the action of emmenagogue oils agree with the results of other observers on the excised uterus of other mammalia. It would seem that the emmenagogue oils in very small amounts have no action at all on the uterus. In higher concentrations such as never could be reached in the blood without producing dangerous, probably fatal, poisoning, they inhibit the uterine movements. When abortion occurs after their use it is probably an indirect result of severe irritation and inflammation of the bowel and kidney. This may induce congestion and reflex movements of the uterus which may in some cases result in abortion. The absence of specific stimulant action of these oils on the uterus renders them all the more dangerous poisons, as, after their failure in ordinary doses, large doses are sometimes taken, resulting in frequent poisoning, in a large proportion of cases, without the production of abortion.

Gynecologic Backache.—A small volume might be written about backache if this symptom were studied exhaustively from every viewpoint, and a most interesting and instructive treatise it would be. Probably the longest chapter should be written by the orthopedist, but the gynecologist, neurologist and internist could contribute much interesting material, and so interdependent should these be that the authors would do well to consult each other freely in the preparation of their respective monographs. Some surprising observations made in the postoperative follow-up clinic at the Woman's Hospital in New York during the past few years led BULLARD (*New York Med. Jour.*, 1921, cxiii, 142) to feel that an analytic study of backache would be interesting. As a result of such an investigation he found that in a series of 721 cases of backache studied, 85 per cent. were cured by an appropriate operation. About 15 per cent. of this series presenting one or more common gynecologic causes of backache were not relieved of the backache by anatomically satisfactory operations. Probably much more than 15 per cent. of the backache in females is not gynecological. This study suggests that 15 to 20 per cent. of all women with retroversion, prolapse, pelvic inflammation, obstetrical lacerations, or pelvic tumors, do not have backache. Closer coöperation with the orthopedist, internist and the neurologist should enable the gynecologist better to diagnose and treat backache in women.

Tuberculosis of the Kidney in Women.—The results of an analytic study of renal tuberculosis in women made by BRADY (*Bull. Johns Hopkins Hosp.*, 1921, xxxii, 13), of the Johns Hopkins Hospital, shows that in a series of 77 patients, 25, or 32 per cent., of the patients complained of hematuria, and in 8 of these it was the first symptom. Two patients first noticed general weakness, and in all the other cases dysuria and pyuria were the first evidences of kidney disease. The general physical examination showed pulmonary tuberculosis in 6 cases. Four of these patients had active, two inactive, pulmonary tuberculosis. One patient developed tuberculous peritonitis two years after the removal of a tuberculous kidney. In 4 cases only was a marked enlargement of the kidney noted, and in all these cases operation revealed that they were dealing with cases of tuberculous pyelonephrosis. The routine gynecologic pelvic examination showed the ureter to be thickened and tender in 23 cases. This nodular thickening, with tenderness of the portion of the ureter which can be felt on vaginal examination, has been of great help in promptly directing attention to the probability of tuberculosis in the urinary tract. In 5 cases surgical treatment was not advised and in 2 others was refused by the patient. Four of these women had tuberculosis of both kidneys, one with symptoms dating back eight years, the second two years, the third one year, and the fourth only eight months. One of these women died in three months, the second in six months, the third in one year, and the fourth left the hospital unimproved and has not been heard of since. One woman had a unilateral renal tuberculosis, with advanced pulmonary changes, and in her case operation was not advised; she also left the hospital unimproved and has since not been heard of. In the two operable cases in which surgical treatment was refused the patients died within one year after leaving the hospital. In 70 out of the 77 cases operations were performed. In 67 cases the kidney was removed and in 3 cases simple nephrotomies were done. The results obtained in these 3 cases are very discouraging. One woman died in three months, a second in two years, a third left the hospital unimproved and has not been heard of since. This means that 8, or 19.5 per cent., of the 42 women of whom the records are complete are now dead. These 8 patients lived, on an average, for three years after their operation. Two of the living patients are unimproved, one three, the other nine years after operation. Seven may be classed as greatly improved. These seven women are all able to carry on their daily occupations and complain of slight bladder symptoms. Twenty-five, or 59.5 per cent. of these women, whose present condition is known are entirely well, with an average of eleven years since their operation. In this series there is one woman operated on twenty-four years ago, another twenty-two years ago and two twenty years ago. These patients have been relieved of all their symptoms by operation and report themselves to be now in good general health. Brady has divided all the cases in which the final results are known into two classes, one formed by those women from whom only the kidney was removed and the other by those from whom as much of the ureter as possible was removed at the same time. After careful study, the writer has been unable to show that the removal of the ureter makes any difference in the ultimate results of the operation. Approximately 19 per cent. of both groups of patients are now dead, 5 per cent.

are unimproved and 76 per cent. are either greatly improved or well. This study, however, has shown that the postoperative sinuses of the patients on whom nephro-ureterectomies were performed healed in an average time of five months, whereas the women in whom the diseased ureters were left, drained for eleven months. From this it would appear that it is better to remove the ureter along with the kidney when the condition of the patient warrants prolonging the anesthetic the short time necessary for carrying out this procedure.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Studies on Experimental Pneumonia.—The experimental study of lobar pneumonia has long been hampered by the difficulty surrounding the production of this disease in animals. The various attempts at introducing bacteria into the deeper air passages by insufflation and by injection in fluid suspension have resulted in bronchopneumonias. Even the highly artificial method of flooding the lung with a suspension of bacteria failed to produce the typical lobar pneumonia. Following a method used by Opie and others in unpublished experiments, BLAKE and CECIL (i, *Jour. Exper. Med.*, 1920, xxxi, 403) were able to produce typical lobar pneumonias in monkeys. The method was by inserting a dry, sterile needle into the trachea and injecting very small doses of living, virulent pneumococci. The organisms were always suspended in 1 c.c. of fluid. All the biological types of pneumococci were employed. The following is a brief summary of the results obtained with the different biological groups of pneumococci: Out of 31 monkeys injected with type i, 26 took lobar pneumonia. Out of 2 monkeys injected with type ii, 2 took lobar pneumonia. Out of 3 monkeys injected with type iii, 3 took lobar pneumonia. Out of 4 monkeys injected with type iv, 1 took lobar pneumonia. All monkeys injected with types ii, iii and iv recovered. Out of 6 monkeys exposed to contact infection only 1 developed lobar pneumonia. Inoculation of pneumococci into the nose and throat induced a carrier state but none of these animals contracted lobar pneumonia, nor did they develop any infection of the upper respiratory tract. Subcutaneous and intravenous injection of pneumococci did not produce lobar pneumonia. Invasion of the blood stream by pneumococci was demonstrated to be secondary to the infection of the lung. They have shown, therefore, that lobar pneumonia is bronchiogenic in origin. Pneumococci were isolated from the blood stream within six hours after the intratracheal

injection. The methods of study after inoculation were similar to the ordinary clinical methods. They consisted in observation and record of clinical symptoms and physical signs, with temperature records made twice daily and daily white cell and differential blood counts, and blood cultures. These records were in every way comparable to those obtained in the course of a lobar pneumonia in the human. Autopsies on the animals that died and on others killed at selected intervals furnished the material for the experimental study of the pathology of the disease. In the report of this work (ii, *Jour. Exper. Med.*, 1920, xxxi, 445) is included the study of 40 autopsies on monkeys. Of these 27 died during the active stage of the disease, or from complications, and 13 were killed at varying intervals following the crisis. This series of animals permitted study of the lungs at intervals of one to twenty-three days after the onset of the disease. This series presented examples of the four classical stages of the disease. Animals dying within five days after intratracheal injection showed either engorgement or red hepatization. The later stages have been thoroughly studied in human material. It is from the study of the early stages that this phase of the problem attains its chief interest. Microscopic examination showed that while the infection invades by the bronchiogenic route, it soon becomes interstitial at some point near the hilus of the lung, producing an early, acute inflammatory reaction in the vascular adventitia and walls of the bronchi near the root of a lobe. This is accompanied by edema and a leukocytic infiltration of the interstitial tissues and by intense capillary engorgement. At this stage bacteria were found to spread rapidly throughout the lung, following the ramifications of the vascular and bronchial trees and appearing always to precede cellular exudation into the alveoli. In the same way hepatization was found to spread throughout the lobe from the region of the hilus to the periphery. During this early process the epithelium of the bronchial tree appears fairly intact and the air passages contain little or no exudate. After the five-day period, in which time the stage of red hepatization has developed, the more familiar histological pictures of lobar pneumonia appeared. The earliest exudate in the alveoli consisted of a few large mononuclear cells and quantities of coagulated serum. Polymorphonuclear leukocytes, more large mononuclear phagocytic cells, and red blood cells are shortly added to this and appear imbedded in a mesh-work of fibrin. The red color of the lung would appear from these studies to be largely due to the engorged capillaries than to free blood. At this time the interstitial lesions were much less prominent than before red hepatization had occurred. The margins of the advancing consolidation continued to show a primary interstitial character of the lesion, and the lumina of terminal bronchioles at the margin were clear of exudate while those lying within the consolidated area contained an exudate like that found in the alveoli. The transition from red to gray hepatization began in the oldest areas of consolidation near the hilus. The picture here was the familiar one so often encountered in lobar pneumonia. At this stage the interstitial reaction had become much less conspicuous. And, as is true in lobar pneumonia in the human, necrosis of the alveoli structure and air passages and thrombosis of vessels were not found. The animals dying late in the disease, or killed shortly after clinical recovery, showed the alveolar exudate to be

undergoing rapid disintegration. It was in every way similar to the picture of resolving pneumonia in the human. Finally it was interesting to note that along with resolution a variable degree of organization was always found. This was present in the perivascular tissues though variable in amount, and likewise to some degree about the bronchi. There were some instances of organization of the exudate. The newly formed fibrous tissue was found covered by a thin layer of epithelium apparently derived from the alveolar lining. The pathogenesis of lobar pneumonia as described by these authors is best followed by briefly reviewing their findings as to the presence of pneumococci in the tissues. While pneumococci were never found in the air passages save after the development of red hepatization in the surrounding tissues, they were demonstrated beneath the bronchial epithelium and in the peribronchial and perivascular stroma three hours after an intratracheal injection. Further, in 2 monkeys, with abortive attacks of pneumonia (recovery on third and fourth days respectively), autopsies immediately after recovery showed a purely interstitial pneumonia without hepatization. The spread of pneumococci from the initial site of invasion of the interstitial tissues near the hilus was entirely by interstitial tissues and lymphatics as far as the alveolar walls where they may be seen prior to an exudation into alveoli. And pneumococci were found free in alveoli as soon as the serous exudate appeared there, and before there was any cellular exudate. They therefore preceded any development of hepatization. During the progress of the above work a considerable amount of spontaneous pneumonia occurred among the stock monkeys. (iii, *Jour. Exper. Med.*, 1920, xxxi, 499). Where possible these were studied clinically and autopsies were performed in all fatal cases, the bacteriological findings in heart's blood, lung, and bronchi being worked out at the same time. It is interesting and definitely in support of the experimental method, to note that spontaneous lobar pneumonia in monkeys is identical with that produced by intratracheal injection of pneumococci, and with lobar pneumonia in man. The outbreak further was shown to have epidemiological interest in that it illustrated how the spread of infection by contact may be accomplished when conditions are favorable. In conjunction with the production of experimental pneumonia in monkeys, Blake and Cecil (iv, *Jour. Exper. Med.*, 1920, xxxi, 519) studied the results of prophylactic vaccination against pneumococcus pneumonia in monkeys. Both saline vaccine and lipovaccine made from a strain of pneumococcus type i were employed. The former gave better results; at least it appeared to have a favorable action in preventing pneumococcus septicemia. No protection was afforded by either type of vaccine against subsequent attacks of pneumococcus pneumonia, and no cross protection against other types of pneumococcus could be demonstrated. The development of active immunity against experimental pneumococcus pneumonia in monkeys following vaccination with living cultures of pneumococci was also tried (v, *Jour. Exper. Med.*, 1920, xxxi, 657). This method has been shown by various workers to have some success against other pathogenic bacteria, and the facility with which monkeys could be exposed to experimental pneumococcus pneumonia made them an excellent subject for the study of the method in pneumococcus infection. Both virulent and avirulent strains were employed, the latter in large doses. It was

found that either strain used as a living vaccine in appropriate doses protected monkeys against experimental pneumonia due to the same type of pneumococcus. And a certain amount of cross immunity is conferred by vaccination with cultures of pneumococcus type i. This method is not without its dangers, as a severe and even fatal pneumococcus septicemia frequently followed the use of a vaccine made from virulent pneumococci. It is noteworthy, too, that the active immunity against pneumococcus produced by this method of vaccination, appeared to be independent of the presence or absence of agglutinins or protective bodies in the serum. The animals which recovered from experimental pneumococcus pneumonia were tested for the degree of active immunity conferred by the disease itself (vi, *Jour. Exper. Med.*, 1920, xxxi, 685), by a second intratracheal inoculation. It was found that a high degree of immunity against the homologous type had been obtained, but that little protection was afforded against other types. As regards type iv pneumococcus pneumonia there was no appreciable immunity against the same or homologous strains of pneumococcus type iv. A study was made of the efficacy of type i antipneumococcus serum in the treatment of monkeys with experimental type i pneumococcus pneumonia (vii, *Jour. Exper. Med.*, 1920, xxxii, 1). It was found that intravenous injection of this serum promptly and permanently cleared the blood of pneumococci, shortened the course of the disease, and greatly modified its severity. Better results were obtained when the serum was administered early and at frequent intervals. When the serum treatment was started later in the course of the disease it was found necessary to continue the injections of the serum over a longer period. It is worth while to note that the control animals in these experiments all died and, further, that normal horse serum exerted no beneficial effect. Since particular interest attaches to the pathology of hemolytic streptococcus pneumonia following recent epidemics of this disease, Blake and Cecil considered that it would be of value to attempt the experimental production of this type of pneumonia (viii, *Jour. Exper. Med.*, 1920, xxxii, 401). The same method of experimental infection was carried out, but as the hemolytic streptococcus is much less virulent for monkeys, it was necessary to use a larger dose of organisms, the organisms from 0.1 c.c. to 10 c.c. of an eighteen-hour plain broth culture being suspended in 1 c.c. of fluid for intratracheal injection. Pneumonia was consistently produced in normal monkeys by this method and it had characters comparable with those of hemolytic streptococci pneumonia in man in respect to the clinical history, complications and pathology; that is, an interstitial pneumonia and a confluent lobular pneumonia were both encountered and were frequently found in the same animals. The type of pneumonia appeared to be dependent upon the amount of streptococcus culture injected, since with the injection of a small amount of culture the interstitial type was produced while the confluent lobular type followed the injection of a large amount of culture. The former was characterized pathologically by a cellular reaction, chiefly of mononuclear type in the framework of the lung. The blood remained sterile. The latter, following the injection of the organisms from 5 c.c. or more of culture, showed a confluent lobular distribution of the pneumonic exudate with areas of lax consolidation. There was a mononuclear cell reaction, and a proliferation of fibroblasts and alveolar

epithelium. With very large doses the tissue showed less evidence of resistance. The pneumonia had a lobular distribution, but the areas of exudate were widespread and confluent and the lung tissue involved showed all grades of reaction from edema to consolidation. The striking point of difference between this and pneumococcus pneumonia is seen in the power of the streptococcus to produce marked local injury to the tissue resulting in extensive damage to the walls of the bronchial tree and in widespread areas of alveolar necrosis. Further, as an end-result, there was a tendency for extensive organization to take place. In these cases a terminal invasion of the blood stream by streptococci occurred. The mode of invasion of the lung was the same as with pneumococcus pneumonia, though the type of reaction thereafter had the important differences noted. These writers differ with McCallum in regard to the pathogenesis of streptococcus pneumonia, indicating that the infection invades at or close to the hilum as in pneumococcus pneumonia and is not a primary terminal bronchiolitis. Finally, they found that irritation of the bronchial tree by chlorine gas or lowering of the animal's natural resistance by an intraperitoneal injection of *Bacillus influenzae* prior to the intratracheal injection greatly facilitated the invasion of the lungs by *Streptococcus hemolyticus*. In continuation of the experimental studies of acute respiratory diseases, the effect of inoculation of *Bacillus influenzae* into the upper respiratory tract as well as by the intratracheal route next claimed the attention of these investigators. The two final papers of the series (ix, *Jour. Exper. Med.*, 1920, xxxii, 691, and x, *Jour. Exper. Med.*, 1920, xxxii, 719) are devoted to the report of this work. A strain of influenza bacillus isolated from the pleural exudate in a case of pneumonia with empyema following influenza was utilized in this work. The virulence of the culture was raised by passage through a series of mice and monkeys. In those animals in which the nasal mucosa was swabbed with a culture of *Bacillus influenzae* an acute respiratory disease followed in most instances. This was of short duration, lasting from three to five days, and was characterized by sudden onset with prostration, the development of sneezing and a cough due to rhinitis and a tracheobronchitis. The febrile reaction was variable and the white blood cell count showed a leukopenia, or sometimes no change. An acute purulent sinusitis was a common complication. In certain of these animals hemorrhagic edema of the lungs, bronchiolitis, and bronchopneumonia also developed. In those receiving the injection of virulent *Bacillus influenzae* directly into the trachea, an experimental bronchiolitis and hemorrhagic bronchopneumonia developed in three out of five animals injected. In either type of experimental *Bacillus influenzae* infection the influenza bacillus could be recovered by culture in the acute stage either pure or associated with other bacteria. In general, both clinically and pathologically, the processes closely resembled on the one hand simple influenza, and on the other uncomplicated *Bacillus influenzae* pneumonia in man. It is noteworthy that experimental *Bacillus influenzae* infection can be initiated by a simple swabbing of the nasal mucosa. This indicates a property of invasiveness not possessed by the pneumococcus or by the *Streptococcus hemolyticus*, as this method of experimental infection with these organisms was shown in the earlier papers to be unsuccessful. Another characteristic difference between *Bacillus*

influenzæ and pneumococci or *Streptococcus hemolytic* infections is seen in the mode of extension in the respiratory system. Inoculated into the upper air passages it extended throughout the mucosal surfaces of these regions, with the result that sinus infections were frequent; here we have another point of resemblance to the disease in man. Further, it was even shown in a number of instances that the simple instilling of cultures of *Bacillus influenza* into the upper air passages also resulted in its extension downward to the finer ramifications, with the development of a terminal bronchiolitis followed by acute inflammatory edema and bronchopneumonia. This mode of spread by continuity along the epithelium of the air passages is in direct contrast to the mode of extension in the case of pneumococcus or *Streptococcus hemolyticus*, in which the organisms early invade the lymphatics and subsequently extend in these channels. These latter experiments are advanced as evidence in favor of the etiologic relation of *Bacillus influenza* to influenza. As the authors state, it seems reasonable to infer from this work that the influenza bacillus is the cause of influenza. They add, however, that a definite conclusion is not permissible, since it is impossible to determine whether the experimental disease is identical with it or only similar to it.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Investigations of the Germicidal Value of Some of the Chlorin Disinfectants.—TILLEY (*Jour. Agri. Research*, October 15, 1920, No. 2, vol. xx) found that in the ordinary routine work of general disinfection, such as disinfection of cattle cars and pens, there is always a large amount of organic matter present. It is evident, therefore, that because of the enormous diminution in germicidal value on addition of organic matter, as well as because of the injurious effects on metals and fabrics, the chlorin disinfectants, as a class, do not seem to be suited for use under the usual conditions and by the usual methods of general disinfection. That is not to say, however, that when properly used they are not efficient and valuable in the treatment of infected wounds; in fact, the evidence available goes to show that they are of great value when so used; and, of course, chlorin and hypochlorites are being very widely and successfully used for the disinfection of drinking water. Compared on a basis of weight of chloramin-T as against the weight of chlorin, as sodium hypochlorite

(Dakin's solution), or hypochlorous acid (eusol), or as chlorin in aqueous solution, chloramin-T is less efficient than the others. But if the comparison is made on the basis of available chlorin contained it is much more efficient against *Staphylococcus aureus*, much less efficient against *Bacillus pyocyaneus* and approximately equal in efficiency against *Bacillus typhosus*. The experiments upon *Bacillus tuberculosis* indicate that the chlorin disinfectants are worth very little so far as that organism is concerned. This is not surprising in view of the use of antiformin ($\text{NaOCl} + \text{NaOH}$) in isolating tubercle bacilli. In the present work, considered as a whole, there is seen throughout more or less "selective action" on the part of the various disinfectants. The most clearly defined example of this is seen in the extremely high value of chloramin-T against *Staphylococcus aureus* as compared with its extremely low value against *Bacillus pyocyaneus*. The results of the experiments upon anthrax spores show that the germicidal action of chlorin compounds is not always so speedy as is commonly supposed, but may extend over several days. The addition of ammonia to solutions of chlorin or hypochlorites very greatly increases germicidal activity and tends to prevent depreciation in value on the addition of organic matter.

Streptococci Occurring in Sour Milk.—JONES (*Jour. Exp. Med.*, January 1, 1921, No. 1, xxxiii, 13) states that a well-defined group of rod-like and coccoid organisms arranged in chains and pairs has been encountered in sour milk. The group comprises at least three species; the largest number ferment dextrose, lactose, maltose, mannitol and salicin, and fail to ferment saccharose, raffinose and inulin. A smaller number ferment saccharose in addition to dextrose, lactose, maltose, mannitol and salicin. A few fail to attack mannitol. All three types grow luxuriantly at room temperature, coagulate milk, reduce litmus, and produce large amounts of acid in fermented bouillon containing dextrose. Specific morphologic and cultural differences exist between the lactic acid streptococci and those associated with mastitis and those occurring in the udder. The lactic acid organisms outgrow the udder streptococci in the milk-souring process. When both types are implanted in sterile milk the udder type soon disappears.

Fate of Microorganisms Introduced into Isolated Loops of the Intestine.—EISKAMP and PARK. (*Jour. Infect. Dis.*, January, 1921, No. 1, xxviii, 67) state that many specific microorganisms injected into isolated loops of the intestine of dogs are destroyed in periods ranging from two to seven hours. This destruction is not due to the antagonistic action of the normal intestinal flora. There is evidently a distinct antibacterial mechanism in the intestine, the nature of which is at present unknown.

Commission on Milk Standards.—The report (*Public Health Reports*, December 10, 1920, No. 50, xxxv, 2955) approves of pasteurization of milk as follows: "(a) That pasteurization of milk should be between the limits of 140° F. and 155° F. At 140° F. the minimum exposure should be twenty minutes. For every degree above 140° F. the time may be reduced by one minute. In no case should the

exposure be for less than five minutes. (b) In order to allow a margin of safety under commercial conditions the commission recommends that the minimum temperature during the period of holding should be made 145° F. and the holding time thirty minutes." Under the head of "Scurvy" the reduction of vitamins by pasteurization is recognized and the use of an antiscorbutic is recommended with the pasteurized milk. In the consideration of dried milk a liberal policy is recommended, as indicated by the following: "WHEREAS, The commission is fully convinced that an increased consumption of milk in its various forms would be highly advantageous to the public health; and WHEREAS, The production and sale of dried and remade milk tend to increase, stabilize and conserve the milk supply; and WHEREAS, All evidence now available favors the view that properly prepared dried milk may be regarded as of nutritional value equal to milk of light grade and that the vitamin content of dried milk and pasteurized milk is substantially the same: THEREFORE BE IT RESOLVED, that the Commission urge upon the health and food control officials a liberal attitude such as shall encourage and not hamper the dried milk industry."

Accuracy of the Schick Reaction.—ZINGER (Jour. Am. Med. Assn., November 13, 1920, No. 20, lxxv, 1333) states that the accuracy of the Schick test depends on the strength of the toxin, the technic of the test and the interpretation of the reaction. Errors in any of these may make the results of the test unreliable. It is possible to guard against a poor technic and a wrong interpretation of the reaction, but it is essential to be able to depend on the accuracy of the outfits for the Schick test obtainable on the market. The outfits furnished by four commercial laboratories were tested. Of five outfits of one laboratory, two contained too small an amount of toxin to give a positive reaction in Schick-positive children. Of three outfits of the second laboratory one was somewhat weaker and two very much weaker than the standard outfit, so that negative reactions were obtained in Schick-positive individuals. The outfits of the third laboratory compared fairly well with the control in the clinical test when twice the amount of toxin dilution prescribed in the directions on the outfits was injected. The animal test showed only about 85 to 90 per cent. of a minimal lethal dose in an outfit instead of one minimal lethal dose. The outfits of the fourth laboratory gave reactions similar to those noted with the control test. The outfits furnished by the Research Laboratory of the Department of Health of New York City gave practically uniform results clinically and the animal test showed full potency of the toxin. It is practicable to manufacture outfits for the Schick test on a large scale without sacrificing accuracy.

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ORIGINAL ARTICLES.

THE SYMPTOMATOLOGY AND DIAGNOSIS OF FOREIGN
BODIES IN THE AIR AND FOOD PASSAGES. BASED
UPON A STUDY OF 789 CASES.¹

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As an example of the importance of this subject the fact may be cited that the most frequent cause of the failure to diagnosticate foreign bodies in the lung, as shown by the case histories in the Bronchoscopic Clinic is that the practitioner is misled by the almost total absence of symptoms during the first few days or weeks. One estimable practitioner went so far as to assure a patient who had aspirated a large metallic foreign body (double pointed fence staple, Case No. Fbdy. 409) that such a thing was impossible, as it would have caused death in five minutes. There were no symptoms for four weeks in that case. The hitherto relative rarity of the cases in the experience of any one observer has prevented systematic study. Since the earlier publication a vast symptomatologic material has accumulated in the Bronchoscopic Clinic and additional data on physical diagnosis² have been gleaned, sufficient I think, to establish now a definite working basis. For the wonderfully able analysis of these data and their presentation in this paper I

¹ Read at the meeting of the American Laryngological, Rhinological and Otological Society, Boston, Mass., June 2, 1920.

² Jackson, Chevalier: See John W. Boyce and others in *Peroral Endoscopy*, 1914. VOL. 161, NO. 5.—MAY, 1921.

am indebted to my assistant, William H. Spencer. To him also credit is due for careful study of the signs and symptoms in all cases coming to the clinic during the last three years. His localizations by physical signs alone have been marvellously accurate in cases of foreign bodies in the trachea and bronchi and his observations are embodied herein. Consultations with Thomas McCrae have developed important findings which are elsewhere published,³ and which for completeness are incorporated herein. Edwin E. Graham, who saw a number of cases in consultation, has published an interesting summary of the pediatric phases of the subject.⁴

SYMPTOMS OF FOREIGN BODY IN THE LARYNX.

It would seem that laryngeal symptoms should always be present at the time of aspiration of a foreign body through the larynx into the lower air passages, and it is true that the majority do give a history of varying degrees of irritation, spasm or obstruction of the larynx. There are, however, a very considerable number of cases in which no laryngeal symptoms are noted at any time, the foreign body probably passing through the larynx so quickly as to cause no irritation, as expressed by a girl of fifteen (Case No. Fbdy. 768), from whose bronchus a large open safety-pin was removed, "It went down like a drink of water." The history of the initial laryngeal spasm or paroxysm is, however, of most important diagnostic significance. The foreign body may be arrested at the entrance to the lower air passages and its presence may result in unconsciousness and even in death with the rapidity of a lightning stroke. Accounts in the daily press of the sudden choking to death of children while playing with beans, toys or what not are by no means infrequent. The author has a large collection of clippings reporting such accidents. Expulsion of the laryngeally lodged object is the happiest termination of this accident which many times happens, as almost everyone can testify from personal experience. The object may be of such size and shape as not completely or seriously to obstruct the glottis, and a relative degree of toleration may be established. *Cough*, at first severe, subsides after a short time, but may persist and become croupy. I have often noted severe distressing cough on insertion of the bronchoscope without an anesthetic, general or local, yet the cough would subside in a few minutes afterward, with the tube continuously in place. A triangular portion of the sternum of a chicken was removed from the larynx of a boy of eight years (Case No. Fbdy. 706), where it had lodged for twenty-five days, causing only a slight degree of stridor

³ McCrae, Thomas: The Physical Signs of Foreign Bodies in the Bronchi, AM. JOUR. MED. SC., March, 1920, No. 3, clix, 313.

⁴ Graham, Edwin E.: Foreign Bodies in the Air and Food Passages, AM. JOUR. DIS. OF CHILDREN, February, 1920, xix, 119-133.

and some slight hoarseness. One of the basal angles rested in the posterior and the other in the anterior commissure of the glottis, the apex being down. The noteworthy lodgment in the larynx for four and a half months of a piece of a thin glass from a broken Christmas tree ornament in a child of fifteen months produced no serious degree of dyspnea or other general disturbance other than a marked impairment of phonation and a laryngeal wheeze. There occurred also at times severe paroxysms of coughing simulating whooping-cough. An interesting point in this history was the statement of the mother that on seeing the child gagging and choking she inserted the finger into the mouth in an endeavor to remove the foreign body. This method used so frequently by parents, the patient himself, or, in some case, the doctor, is responsible many times for the entrance of the foreign bodies into the larynx which would otherwise remain in the esophagus or be swallowed, and the trauma thus caused may produce symptoms, especially croupy cough, that mislead by persistence after the foreign body itself has passed on downward into the air or food passages. Guthrie⁵ reports the remarkable sojourn of a piece of rabbit bone, measuring 14 by 21 mm., for eighteen months in the larynx of a girl of eleven years without producing sufficient reaction to cut off the airway completely. This is, however, not the usual course of events, for prompt reactionary swelling of the larynx usually renders breathing so labored that inspection of the larynx is called for and the intruder is discovered and removed.

Dislodgment and the passage downward of the foreign body may completely relieve the laryngeal symptoms if the stay of the intruder in the larynx has been brief. Often some laryngeal irritation persists for a time as an evidence of the duration of the laryngeal lodgment. As an indication of the toxicity of the peanut, marked subglottic swelling was observed in a girl of five years, three hours after the aspiration of half a kernel of a jumbo peanut. The parents stated that the initial paroxysm of cough, dyspnea, cyanosis and vomiting lasted for a half hour, then suddenly subsided (Case No. Fbdy. 769).

Recurrence of the laryngeal paroxysms suggests the lodgment in the larynx of a movable foreign body or it may result from the coughing of a movable foreign body in the trachea up against the under surface of the chords. One must always keep in mind sudden asphyxia from a possible lodgment in the glottic chink of a large tracheal foreign body which has been forced upward by bechic powers or by attempts made to aid in expulsion by holding the patient head down and feet up.

The *subjective sensation* of an intruder is usually present in cases of a laryngeally lodged foreign body during the first days of lodg-

ment. There is often also rather sharp *pain* near "Adam's apple" or referred to one or both ears. If the arytenoid region is affected there may be *odynophagia*, or the patient may complain of pain of a piercing character on swallowing, due to movement of the object during the closure of the larynx. This has often led to the mistake of diagnosing esophageal lodgment. Irritative croupy cough is usually present and is often unproductive. *Phonation* is apt to be seriously impaired, although aphonia is not common. The sputum may be blood-streaked, and in those localities where leeches abound the not infrequent attachment of a leech to the larynx is productive of copious hemoptysis. *Dyspnea* varies in degree with the size of the intruder and with the degree of swelling it produces by its presence in the larynx. There is usually a distinct laryngeal stridor, which with the dyspnea immediately suggests diphtheria to the practitioner and for which, in case of doubt, he wisely administers diphtheria antitoxin. Fever and general disturbance are usually absent unless a perichondritis of the laryngeal cartilages is present. Tooth brush bristles, fish bones and other small and pointed objects may become forced beneath the mucosa and cause this distressing condition with its sometimes disastrous destruction of the framework of the larynx and its usual sequel of laryngeal stenosis.

The diagnosis of laryngeal foreign bodies in infants and young children depends much on the history. The sudden onset of signs of laryngeal obstruction during apparent perfect health is rarely found in disease; though patients sometimes say the onset was sudden in laryngeal disease of considerable duration and in some cases of foreign body the obstruction does not set in at once. If the child were known to have had some object in its mouth previous to the onset of the symptoms the diagnosis is rendered almost certain. Adults, of course, can usually give definite history of the accident, although the aspiration may occur during narcosis or unconsciousness. In children the object may have been inhaled during an unwatched moment. Every case of suspected foreign body should be radiographically studied and plates made in the lateral as well as anteroposterior positions. This study should be made even though the object may be thought not to be radiopaque, for it has been our observation that the patient and parents may be mistaken in the identity of the foreign body—what was thought to be a fragment of bone may prove to be a piece of solder, tin or enamel-ware, etc. It is remarkable with what clearness the details of the larynx and trachea may be shown by a skilful roentgenologist and in many cases even non-metallic foreign bodies can be definitely shown.

Diphtheria is the disease most liable to be confounded with laryngeal foreign body lodgment. The error has occurred both ways—diphtheria being mistaken for foreign body, and *vice versa*.

The administration of antitoxin is wisely done in cases of doubt while waiting to complete the diagnosis.

Hoarseness in angioneurotic edema involving the larynx may simulate in rapidity the symptoms of laryngeal foreign body, but there will be the history of previous symptoms of the condition in other parts of the body, and perhaps also in the larynx. Edema of the larynx from other general conditions will be of slower onset, and study will reveal the basic factors. Influenzal laryngeal edema occurs, as a rule, during epidemics. First cases in epidemics may not be recognized.

Definite diagnosis can be made with mirror laryngoscopy in adults and with the direct laryngoscope in children. All preparations for removal of the foreign body by bronchoscopy and for tracheotomy should be made before direct laryngoscopy is attempted in children with suspected laryngeal foreign body, for shifting of the foreign body may cut off the airway, it may be aspirated into the lower air passages where we would wish to follow it with the bronchoscope, or other accidents occur. The facile bronchoscopist will insert the bronchoscope quicker than tracheotomy can be done. It should be emphasized that general anesthesia is to be avoided during removal because of the danger of asphyxia. Sterile swabs for culture material should be at hand, though usually diphtheritic cases, coming as suspected foreign body, are readily diagnosed visually by direct laryngoscopy.

SYMPTOMS OF FOREIGN BODY IN THE TRACHEA.

The glottic chink is much smaller than the tracheal lumen, therefore objects which pass through the larynx are rarely large enough to become impacted in the trachea. A bolus of food may because of its consistency fill the trachea and result in prompt asphyxia, but most tracheal foreign bodies, unless sharp-pointed are movable, and produce a diffuse traumatic tracheitis in their migrations, and may terminate suddenly by asphyxia through impaction in the glottic chink. Organic substances, such as beans, maize and large nut kernels, are frequent tracheal intruders, although any object small enough to pass the glottic chink yet too large to enter either main bronchus may be found.

We have, as a rule, the history of an initial laryngeal spasm which subsides but leaves the patient with a wheezing respiration and a cough. The wheezing is usually louder than that heard in bronchial foreign bodies, and often has a lower pitch than the true "asthmatoïd wheeze." Cough is a most distressing symptom, coming in paroxysms which may be so severe as to produce vomiting. Cyanosis and dyspnea often accompany the cough, and one may perhaps hear a flapping sound as the foreign body moves in the trachea.

The patient can feel the movements of the foreign body and palpation of the trachea will reveal the vibrations of these movements, which may also be heard by placing the stethoscope over the trachea.

If the foreign body be not removed, increasing dyspnea occurs, produced by the swelling of the subglottic tissues and tracheo-bronchial mucosa from the trauma of the object, aided in cases of organic substances by increase in bulk of the object itself, due to the absorption of fluid. Sudden asphyxia is always a danger, for a powerful bechic action may jam the foreign body between the chords. The tracheal area of cross-section being larger than that of the glottis a foreign body may permit air to pass it freely, whereas if jammed in the glottis the airway may be dangerously or even completely occluded. For this reason early removal is often imperative. If the foreign body be pointed, pain may be a symptom, and it may be localized more or less accurately by the patient over the site of impaction. This is rare, but a few such cases have come to the Bronchoscopic Clinic. A foreign body free to move in the trachea will usually cause more cough than a foreign body fixed in one position in the trachea or a bronchus.

The symptoms of tracheal foreign body were well shown in a boy of two and a half years (Case No. Fbdy. 784) who aspirated a kernel of dried maize. There immediately occurred an alarming paroxysm of choking and cyanosis. Wheezing and labored respirations followed and peculiar spasmodic coughing attacks recurred at frequent intervals. The expiratory bechic blast seemed suddenly cut off with a valve-like click, after which inspiratory dyspnea and cyanosis would be present for a short time. The above condition could be produced by lowering the head, and was relieved by placing the child in the upright position. It was plainly due to the impact of the kernel of corn against the under surface of the chords in its migrations in the trachea during coughing. If the child were crying at the time a sudden cutting off of the phonation occurred when the foreign body reached the subglottic region—in a manner so characteristic as to be unmistakable when once heard. A palpatory vibration was present during these coughing attacks and the stethoscope could plainly hear the rumble of the shiftings of the corn. During the intervals between attacks it was easily made out by physical signs that the corn was lodged in the orifice of the right main bronchus, and at these times no dyspnea was present. Spencer after his physical examination assured me positively that the foreign body was loose in the trachea, and at bronchoscopy I so found it. The asthmatoïd wheezing and paroxysmal coughing ceased immediately after the removal of the foreign body. Sudden shutting off of both the expiratory blast and phonation during paroxysmal cough is almost pathognomonic of a movable tracheal foreign body.

SYMPTOMS OF FOREIGN BODY IN THE BRONCHI.

Unknown Presence of Bronchial Foreign Bodies. While the history of an initial laryngeal spasm is of great importance in the diagnosis of a foreign body in the lower air passages, the lack of such a history by no means excludes the possibility of foreign body being present. The inhalation may have occurred in childhood; the accident may have been forgotten or overlooked under stress of emotion; it may have occurred during unconsciousness or under narcosis; for instance, in tooth extraction; the size and shape of the foreign body having been such as to allow its rapid passage through

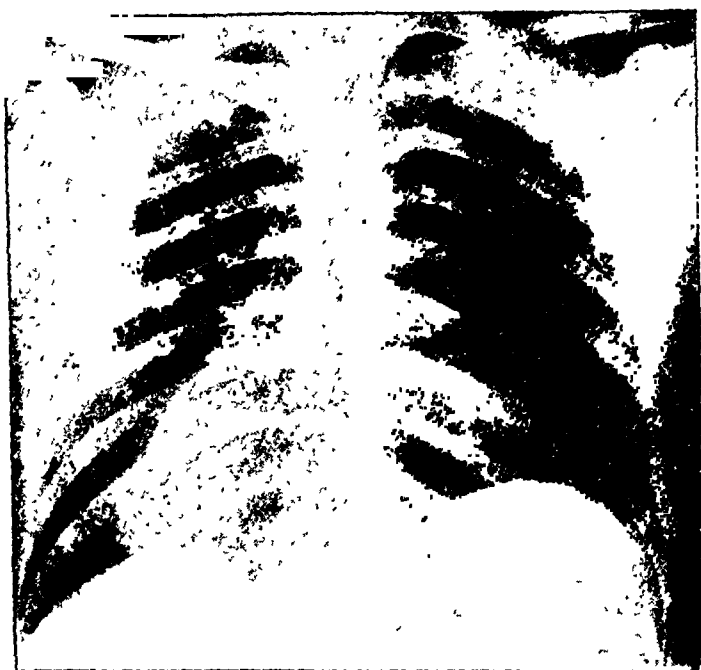


FIG. 1.—Roentgenogram showing pin in right lung of a woman, aged thirty-eight years, admitted dying of pulmonary hemorrhage and showing all other symptoms of pulmonary tuberculosis, but lacking bacilli in the sputum. No bronchoscopy was done. Postmortem showed absence of any tuberculous lesion.

the larynx without causing irritation. Our case histories show many instances in which the presence of a foreign body in the lung was not known until a radiograph was made. A particularly sad case was that of a woman, aged thirty-eight years, who was brought to Jefferson Hospital in a moribund condition due to repeated hemorrhages and sepsis, the result of the presence of an open safety-pin in the right stem bronchus (Fig. 1). She had been treated for tuberculosis for many years, and five years before admission had had a radiograph of the chest which showed the open safety-pin in the bronchus. At the time she was having a remission of symptoms, and her physician, being evidently unaware of the safety and

success of bronchoscopy in such cases, advised against the removal of the foreign body on the principle of "leaving well enough alone." Six months before admission hemorrhages commenced and continued until she was brought to the hospital in an exsanguinated condition, dying the next day. No bronchoscopy was done because of the extreme gravity of the patient's general condition and because the fatal bleeding was not directly due to the pin but to the erosion of a

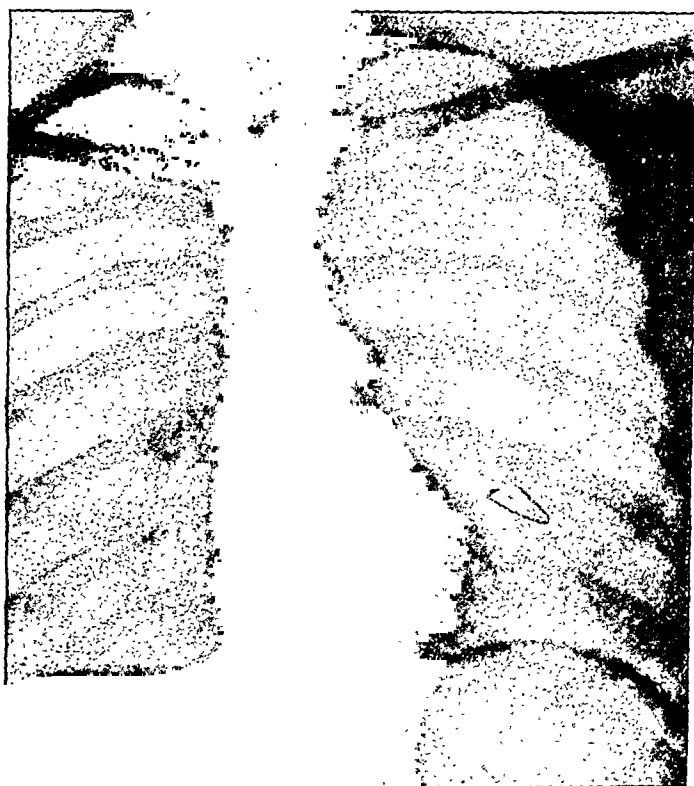


FIG. 2.—Case No. Fbdy. 748. Open bar pin in left lung of a girl, aged twenty-one years. Time of aspiration thought to have been when patient was three years old. Symptoms were those of chronic cough and purulent expectoration. Slight asthmatoïd wheeze present at times. Complete recovery after removal by peroral bronchoscopy, under local anesthesia, in nine minutes fourteen seconds. Plate by Willis F. Manges.

vessel by the suppuration originally started by the pin. Autopsy by E. D. Funk revealed extensive destruction of lung tissue but no tuberculous lesions.

An atomizer tip was unknowingly aspirated into the lung of an adult intelligent business man (Case No. Fbdy. 611⁶) while spraying

⁶ Jackson, Chevalier: See illustration in the Mütter Lecture, Surg., Gynec. and Obst., March, 1919, pp. 201-261.

his own throat. He also had received sanitarium care for supposed pulmonary tuberculosis until a radiograph of the chest revealed the metallic object. Complete recovery of health followed the bronchoscopic removal of the foreign body. It has for many years been my earnest teaching that every chronic chest condition should have the benefit of a radiographic study, even though it be thought tuberculous, but particularly if tubercle bacilli had not been found in the sputum. No more striking confirmation of the value of this procedure can be evinced than the statement of a physician in a Southern State that after the installation of a roentgen-ray apparatus in a tuberculosis sanitarium with which he was connected a routine



FIG. 3.—Case No. Fbdy 659. Roentgenogram showing metallic umbrella-tip very low in the right lung of a boy aged eight years. Entered the lung probably at about two years of age, reaching its low position in six years by pathologic processes. Symptoms: Complete bronchiectatic syndrome. Foreign body unsuspected. Diagnosis by roentgen ray. Peroral bronchoscopic removal without anesthesia. Recovery. Plates by David R. Bowen.

radiographic study was made of about 200 patients, and in one case a bronchial foreign body was found to be the cause of the chest symptoms, there being no tuberculous process present. On the other hand, leaning too heavily on the roentgen-ray laboratory leads to an equally deplorable state of affairs. The author deplores the fact that he for years neglected in many cases to have proper study by a physical diagnostician in cases of foreign body that showed plainly in the ray. Such study should never be neglected because of the great value of physical diagnosis which is our only dependence in non-opaque foreign bodies. Over and over again Spencer has been able precisely to locate by physical signs alone non-opaque foreign bodies.

Latency. After entering a bronchus a metallic foreign body or one of dense non-irritating character which does not completely occlude the lumen may cause no symptoms for a period of weeks or months. It is this period of delusive calm which allays the fears of the patient or parents and gives a false confirmation to the practitioner's assurance that there can be nothing in the lung. Pathologic changes, however, progressively develop and show themselves in an ever-increasing train of symptoms which will ultimately invalidate the patient (Fig. 3).



FIG. 4.—Case No. Fbdy, 645. Roentgenogram showing small electric lamp in left lung of a boy aged six years; left main bronchus tightly "corked." Lamp *in situ* six days; left lung atelectatic; right lung emphysematous. Mediastinum displaced to atelectatic side. These changes were demonstrable by physical signs. Lamp was removed without anesthesia in one minute nine seconds. Roentgenogram at the left was taken ten minutes after removal, and shows air beginning to enter the collapsed lung. Recovery complete in twenty-four hours. Symptoms: Fever, cough, dyspnea, distress. At first thought to be pneumonia. Physical signs: Greatly limited expansion on the left side. Impaired resonance above and flatness below the fourth rib, front and back. Breath sounds intensely tubular, with few fine crackling rales above fourth rib. Below breath sounds very distant and vocal resonance much diminished. Right side of chest hyperresonant, with harsh breath sounds and numerous loud harsh rales. Plates by Arthur C. Sender.

Rapid Onset of Symptoms. If a bronchus is completely plugged reaction is usually prompt and violent even though the foreign body be in itself of a relatively non-irritating nature (Case No. Fbdy. 645, Fig. 4). Organic foreign bodies, such as nut-kernels, especially that of the peanut, are evidenced by marked general toxemia and local reaction in children under two years of age. Within twenty-four hours the child may be gravely ill and may even die. Children over two years of age do not react so severely to the organic objects, whether it is because of their higher degree of resistance or larger air passages and greater hecic powers has not been determined. It is

a well-established fact, however, that the symptoms are in inverse proportion to the age, so that a peanut-kernel in the bronchus of a child aged ten years seems but little more irritating than the denser foreign bodies. To this disease we have given the name "arachidic bronchitis."⁷

Tactile Sense of Bronchial Foreign Body. After the foreign body has invaded a bronchus the patient loses his power to localize it by tactile sensation. It is not unusual for bronchoscopy to be requested because of the supposed aspiration of an object which the patient feels to be present. A number of these requests were from neurotic



FIG. 5.—Case No. Fbdy, 768. Open safety-pin in right main bronchus, spring end at carina, keeper at orifice of middle lobe of bronchus, point in upper lobe of bronchus. Pain localized by the patient in the lower chest and epigastrium, worse on deep breathing and cough. It was especially noted by McCrae on inspection that expansion was decreased on the invaded side, though the foreign body was not obstructive. Plates by Willis F. Manges.

individuals, some of whom had read popularized versions of bronchoscopy in the daily press. The lack of other symptoms and a negative radiographic study should prevent unnecessary bronchoscopy—which in hysterical individuals would but confirm them in their belief in the presence of the foreign body.

Pain in Cases of Bronchially-lodged Foreign Body. Although pain in the chest is a rare accompaniment of bronchial foreign bodies in our experience, there are a few exceptional cases, such as those

⁷ Jackson, Chevalier, and Spencer, William H.: Arachidic Bronchitis, Jour. Am. Med. Assn., August 30, 1919, lxxiii, 672-677.

cited below, in which it has been localized to the site of the intruder. The pain is rarely severe, but is of an annoying, piercing nature, made more intense by deep breathing or coughing. In all of the cases observed a pointed foreign body was present. An interesting history was obtained from a girl of fifteen years who had aspirated a large safety-pin which she was positive as having been closed by her before being placed in the mouth and which she states entered the air-passages with no irritation whatever (Case No. Fbdy. 768). Three days after the accident there occurred, during

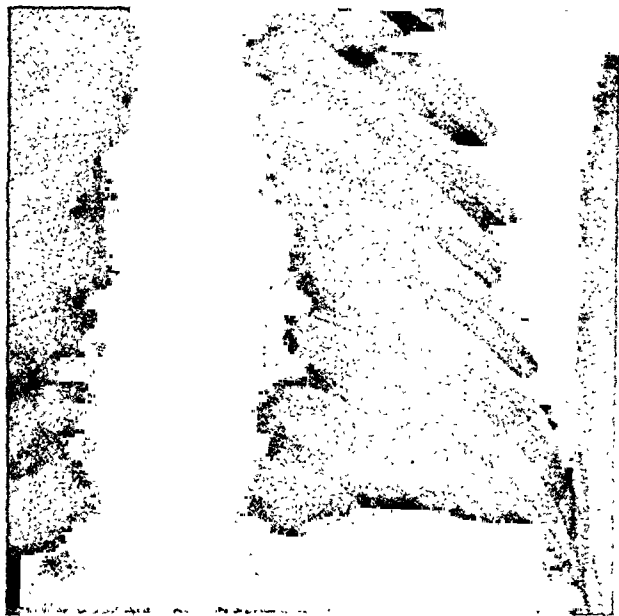


FIG. 6.—Case No. Fbdies. 774-775. Two thumb tacks in right lung. First one encountered in right main bronchus at orifice of upper lobe bronchus. Second tack point downward, the entire bronchial lumen being shut off by the head of the tack. Patient complained of pain in the upper right chest at times in the region of the tacks. Inspection showed limited expansion on invaded side. Markedly diminished breath sounds distal to the foreign body. Peroral bronchoscopic removal of the tacks without anesthesia in five minutes and twenty-eight seconds resulted in immediate disappearance of the pain. Plates by Willis F. Manges.

a coughing attack, a sudden, sharp pain over the location of the foreign body, as shown by the radiograph (Fig. 5) and later during coughing she felt a piercing sensation at this location. The safety-pin was much too large to pass through her larynx open, and point downward, so we must assume that it was closed at the time of aspiration and opened later during a coughing attack. The pin-point was found defective on examination after removal, so that the endobronchial opening was entirely possible.

A boy of twelve years (Case No. Fbdies. 774-775 Fig. 6) was

able, by the pain sense, to localize on his chest wall the site of lodgment of two thumb tacks lying, head together, in the right main bronchus. A woman of forty-eight years (Fbdy. No. 664, Fig. 7), was sent in to have a double-pointed tack removed from the lung. Her main symptom was the sharp, pricking pain at its site of impaction. It seems indicated by my observations that the pain sense is irregularly distributed to certain areas and to a less extent or not at all to others. In all the foregoing cases the location was verified by subsequent bronchoscopic removal from the location indicated by the patient. These cases show that there are at least some



FIG. 7.—Case No. Fbdy. 664. Double pointed staple in left bronchus at orifice of upper lobe bronchus; points upward. The patient localized a dull, aching pain in the fifth left interspace about two inches from the midline. This pain was aggravated by coughing, and after the first few days was referred to the back. Diminished expansion through foreign body was not obstructive. Peroral bronchoscopic removal was accomplished in two minutes thirty-five seconds by version and resulted in immediate disappearance of the pain. Plates by David R. Bowen.

locations in which the pain sense is present and correctly localizable by the patient. These locations are:

1. Left bronchus at orifice of upper-lobe bronchus.
2. Right main bronchus and stem-bronchus from carina to middle-lobe bronchus.
3. Right main bronchus at orifice of upper-lobe bronchus.

Doubtless there are many other localities with equally localizable sensation, but these are cited as definitely proved. In many other cases pain complained of after the patient had seen the ray plate was not recorded because it was obviously psychic.

Diffuse aching sensations throughout the chest are very occasionally observed in bronchial foreign body cases. If the pathology induced by the foreign body reaches the pleura, pain is, of course, a symptom, but one cannot include this as produced by the foreign body itself. George L. Richards (*loc. cit.*) reports a case in which pain in the chest along with an unexplained leukocytosis and the occasional discharge of pus suggested to him the diagnosis of foreign body in the chest, which was later confirmed by a radiograph and the bronchoscopic removal of a tack.

Taste and Odor. One patient, from whose bronchus a much corroded iron carpet staple was removed, complained of an inky taste in the mouth after coughing. The taste and odor of the pus in long retained foreign body cases, in some instances, causes nausea as well as anorexia. Decomposing foreign bodies will be subjectively known to the patient by the taste and odor they induce, though, as in other cases, foul sputum is less noticeable to the patient than to others. After a prolonged bronchoscopy in a foreign body case of long standing the author has often himself had the subjective sense of taste corresponding to the peculiar foul, penetrating, offensive odor resulting from the decomposition of the dead organic material by the saprophytes. This odor and taste differ in character in different cases; but is foul in practically all cases of prolonged sojourn of a foreign body in the lungs. Recent cases of such substances as bones, especially when periosteum or other tissue is attached, give in some cases an objective and subjective odor and a subjective taste to the spectator. In both of these and the long sojourn cases the foulest odors are only mildly offensive to the patient. The author has always found the odor becomes less and less offensive in a prolonged bronchoscopy, unless a new pocket with a different odor is opened up and drained by the bronchoscope. An odorous sputum is strongly suggestive of a foreign body when the question arises as to whether a chronic chest condition is due to tuberculosis or other causes.

Dyspnea. The compensatory power of one lung during bronchial obstruction of its fellow is truly remarkable. Even with no air entering the affected lung the subjective sense of dyspnea is rarely felt. It has been many times observed in the clinic that a recently inhaled foreign body has shifted from one side to the other, each time causing complete blocking of the invaded bronchus, yet the patient was unaware of the change and at no time was short of breath. It is to be emphasized that this holds true only in the case of recently aspirated foreign bodies, for if a bronchus has been blocked for a sufficient time to allow extensive inflammatory changes in the obstructed lung its aërating function is arrested, so that shifting of the foreign body and obstruction of the opposite lung may prove quickly fatal. This is well illustrated by the happenings at bronchoscopy in a child of twenty-one months (Case No. Fbdy. 725 Fig. 8),

who had had a peanut-kernel in the right main bronchus for two weeks. The right lung was the seat of extensive inflammatory reaction and the little one was seriously ill from the toxemia and the diffuse laryngo-tracheobronchitis (arachidic bronchitis) usually



FIG. 8b.—Two days later after removal of peanut. Right diaphragm in practically normal position; right and left lungs show equal density. Abscess density has largely disappeared.

FIG. 8a.—Case No. Tbdy. 725. Peanut kernel in right main bronchus. Wheezing respiration present. Note increased transparency of the right lung. Abscess formation in lower right lobe. Note depression of diaphragm.

associated with peanut-kernels. After the insertion of the bronchoscope a sponge introduced to remove the copious secretion in the trachea caused a hard cough, which was followed by intense cyanosis. After a few gasps for breath, respiration ceased even with the bronchoscope *in situ*, affording a free airway. Insufflation of

oxygen through the side tube of the bronchoscope and artificial respiration were rewarded after three minutes by a return of voluntary respiratory efforts, although the cyanosis did not completely disappear. Careful search of the right bronchus revealed great inflammatory reaction. Much accumulated pus and a few fragments of peanut-kernel were removed. While oxygen was being piped down into the right bronchus the child again became deeply cyanosed and ceased breathing. The bronchoscope was now inserted into the left main bronchus, from which a large peanut kernel was removed, resulting in an immediate disappearance of the cyanosis, restoration of respiration and return to normal. It is apparent that the kernel was dislodged at the time the first sponge was introduced and was reaspirated into the left bronchus, blocking the only aërating organ, the right lung being incapacitated by inflammatory reaction. Had the dislodgment occurred at any other than the fortunate time in which the bronchoscope was in position death would have occurred promptly and inevitably. It is also probable that had the bronchoscopy been performed under general anesthesia respiration could not have been restored. In passing it may be mentioned that in these cases neither anesthetic nor sedative should be administered for the bronchoscopy, because the voluntary respiratory and heclic efforts of the patient are required to free the air-passages from secretion and maintain the respiratory function, even though it be for many seconds interrupted. Prolonged mechanical obstruction to respiration introduces an enormous element of danger to general anesthesia.

Cyanosis is a symptom of suddenly produced dyspnea and is not often seen in case of obstruction produced by a bronchial (not tracheal or laryngeal) foreign body unless under the conditions recited in the above-mentioned case. Slight cyanosis of the fingernails and lips may be present in arachidic cases because of the laryngeal swelling and accumulation of secretions in the bronchi, which interfere with aëration of the blood. Prolonged dyspnea results in death from exhaustion and is evidenced by gradually increased ashy pallor, anxious facies, sweating, restlessness and gradual heart failure. The cardinal signs of obstructive dyspnea—inspiratory retraction of the lower ribs, epigastrium, supraclavicular and suprasternal fossæ—should be carefully watched, their degree of severity and the condition of the heart should decide the urgency of tracheotomy. Children have been allowed to die because the attendant watching the case considered cyanosis the principal sign of severe dyspnea.

Cough, so immediate a symptom in laryngeal or tracheal foreign bodies, is often not developed in bronchial cases for a number of weeks after the inhalation of a non-irritating foreign body, such as one of metal. After this symptomless interval of longer or shorter duration an unproductive, irritative, hacking is usually noticed.

This in some cases becomes more and more severe until the cough racks the patient, interfering with sleep and even producing vomiting. An ever-increasing amount of sputum is expectorated—at first whitish and mucoid, becoming green, yellow and purulent; and as retention increases, in a bronchiectatic or abscess cavity, a foul odor is developed which is most distressing to the patient and friends. A few cases show surprisingly little of both cough and expectoration. In marked contrast to metallic foreign bodies the aspiration of organic substances is followed immediately by paroxysmal, sometimes croupy cough, and the secretion of pinkish-gray purulent sputum. Coughing is attended by dyspnea and cyanosis because of lodgment in the swollen larynx of the thick, mucilaginous pus which is with difficulty expelled by the child. In a recent case (Case No. Fbdy. 787) with arachidic bronchitis, violent, exhausting paroxysms of coughing continued as long as an hour.

Hemoptysis, varying from blood-streaked sputum to copious hemorrhage, is not an uncommon symptom with pointed bronchial foreign bodies. The previously mentioned case of safety-pin in the lung for an unknown number of years resulted fatally from prolonged and repeated hemoptysis. It is well known that the initial symptom of a tuberculous lung involvement may be a pulmonary hemorrhage. An example of the close simulation of the entire tuberculous syndrome by bronchial foreign bodies is seen in the case of a woman, aged forty-one years (Case No. Fbdy. 726, Fig. 9), from whose right bronchus a large bent shawl-pin was removed by peroral bronchoscopy after a sojourn of twenty-eight years. At the age of thirteen, while dressing a doll, she told her parents she had swallowed a bent shawl-pin, and the incident was noted in the father's diary at the time. Because of failure to find the pin in the stools and the lack of symptoms of any nature it was assumed that she had been mistaken. A moderate cough developed but was not considered serious enough to demand medical treatment. The patient married at eighteen and after puerperium was one day found unconscious from severe pulmonary hemorrhage. Recurring hemorrhages kept the patient in bed for five months, after which a gradual convalescence returned the patient to a degree of health, allowing her to assume some of the household duties. The cough, however, became increasingly more severe, and at intervals of a few months, attacks characterized by fever, sweats and malaise would confine the patient to bed until during a severe paroxysm of cough a large amount of pus was expelled. A partial remission of symptoms would then occur. Constant semi-invalidism was her lot and its basis was considered tuberculous by all physicians who treated her. The diagnosis was strengthened by the fact that a brother died from tuberculosis during the course of our patient's illness. Repeated sputum examinations were negative for tubercle bacilli, so that her

physician finally had a radiograph of the chest made, which revealed the pin in the right lung, and he referred the case to the Bronchoscopic Clinic. Under local anesthesia we passed the bronchoscope through the mouth and located the pin in the inferior lobe of the right lung. The pin was withdrawn by forceps through the bronchoscope in three minutes and twenty-five seconds. Removal of the pin in the Bronchoscopic Clinic has been followed by rapid subsidence of the symptoms and a complete recovery. The aspiration

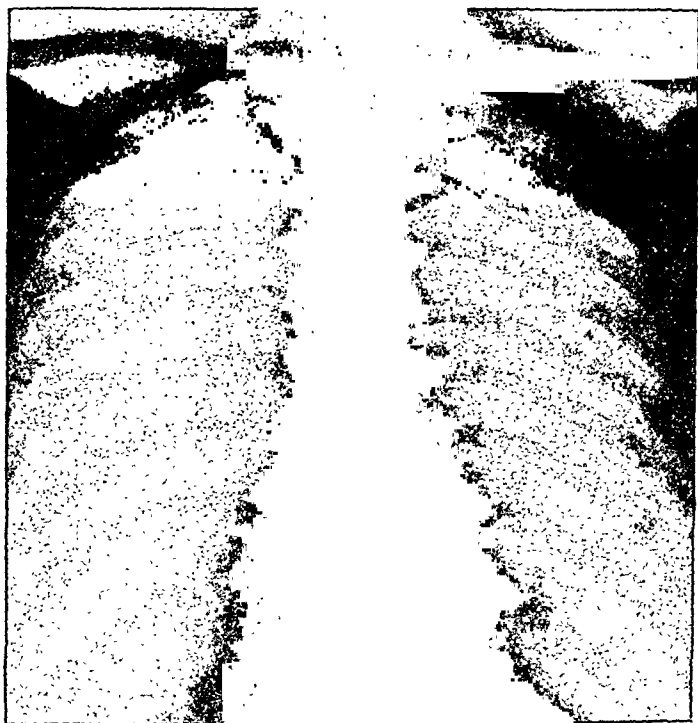


FIG. 9.—Case No. Fbdy. 726. Roentgenogram showing shawl-pin in lung of a woman, aged forty-one years. The pin produced a complete tuberculous syndrome, including copious hemoptysis. Sojourn of foreign body about twenty-eight years. Pin removed through the mouth in three minutes twenty-five seconds by bronchoscopy under local anesthesia. Complete recovery followed.

of the pin at the age of thirteen had been forgotten until it was brought to mind by the radiograph and the record in the father's diary, by which the date was fixed, was searched for and found.

In none of the foreign body cases coming under our observation have tubercle bacilli been found in the sputum. We have come to consider the finding of tubercle bacilli in the sputum, in a chronic chest condition suspected of being due to a non-opaque bronchial foreign body, to be a marked negative factor on the foreign body side of the question. This does not seem logically justifiable in

view of the fact that it is possible for a tuberculous individual to aspirate a foreign body; but the coëxistence of the two has not been met in the entire experience of the Bronchoscopic Clinic.

Fever is a variable symptom in bronchial foreign bodies. With organic foreign bodies, especially peanut-kernels, there is, in the younger patients, marked febrile reaction. The temperature chart shows an irregular course, with the maximum from 102° to 104° . The pulse-rate is usually relatively higher than the temperature, as would be expected from the dyspnea usually present. The respiratory rate increases in proportion to the degree of dyspnea present. Temperature rise is rarely associated with the presence of metallic foreign bodies until extensive inflammatory changes and secondary purulent processes have developed. The history of periodic attacks of fever, chills and malaise suggest the accumulation of pus in an abscess cavity, the spontaneous drainage of which by expectoration relieves the symptoms until refilling occurs. As pointed out by George L. Richards this sequence should always suggest foreign body in the lung. The febrile attacks usually recur with increasing frequency; the quantity of the pus accumulation usually becomes greater and finally offensive in odor, due to saprophytic changes in the pus. Bacteriologic examination of the sputum has revealed all of the usual respiratory-tract organisms except the tubercle bacilli. Bacilli of the colon group frequently account for the odor.

Night-sweats are common in the chronic septic foreign body cases. In fact all of the symptoms of tuberculosis are simulated with such exactitude that the older observers, before the days of knowledge of the specific bacteriologic cause, were fully justified in their statements that retained bronchial foreign bodies caused death from phthisis pulmonalis.

Clubbed Fingers and Toes and Incurving of the Finger-nails are frequently seen in prolonged foreign-body sojourn (see Figs. 10 and 11).

Emaciation is progressive, as a rule, when abscess or bronchiectatic cavity formation is present, yet this is subject to the same variation as in tuberculosis. Rest and a general antituberculous regimen will improve the general condition greatly; gain in weight, cessation of fever and lessening of cough will result, only to be lost again when active life is resumed. As an instance of the fluctuation of the symptoms we may cite the case of one patient (Case No. Fbdy. 608, Fig. 12), who had carried a beef bone in his lung for eleven years, gained fifteen pounds in weight during the seven months before coming to the Bronchoscopic Clinic by the antituberculous regimen of a California sanitarium. Of course, after the removal of the bone gain in weight was much more rapid, but the gain while the foreign body was still in the lung illustrates the important diagnostic point that gain in weight does not negative foreign body.

Opening of the abscess into the pleura, forming a pyopneumothorax, is an unfortunate accident which sometimes occurs—the

foreign body rarely follows the pus into the pleural cavity. Usually it is fixed in its bed by adhesions.

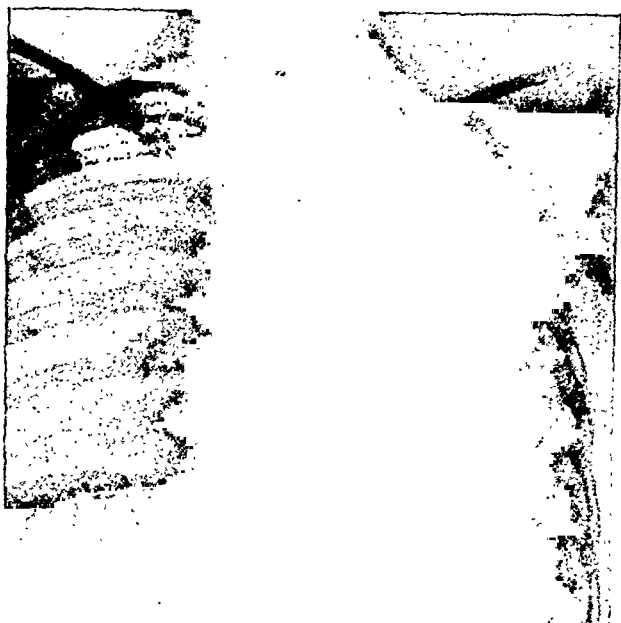


FIG. 10.—Case No. Fbdy. 679. Roentgenogram showing intubation tube in left lung of a boy, aged seven years, where it had been unsuspected for a year and a half. Diagnosis incidental to radiography for chest disease by Dr. Wagner, of the Nesbit West Side Hospital, Kingston, Pa. Faint asthmatoïd wheeze present.



FIG. 11.—From a photograph showing the fingers and toes of Case No. Fbdy. 679 (Fig. 10). This clubbing is a symptom calling for the diagnostic exclusion of a foreign body in every case. In this patient it was part of a syndrome simulating tuberculosis minus the presence of tubercle bacillus. Peroral bronchoscopic removal of an intubation tube from left bronchus without anesthesia required three minutes and fifty-nine seconds, and resulted in complete recovery.

Leukocytosis, as with pus conditions elsewhere in the organism, is found with prolonged foreign body sojourn and also with the acute symptoms manifested when irritating foreign bodies are aspirated into the bronchus. The presence of an increased leukocyte count may be of differential diagnostic value in lung conditions when tuberculosis is to be ruled out, for in tuberculosis a leukopenia is the picture most frequently seen. The association of a moderate leukocytosis with prolonged sojourn of a foreign body has been noted by George L. Richards,⁸ in a case in which he made a diagnosis of foreign body in the lung in the absence of a foreign body history.

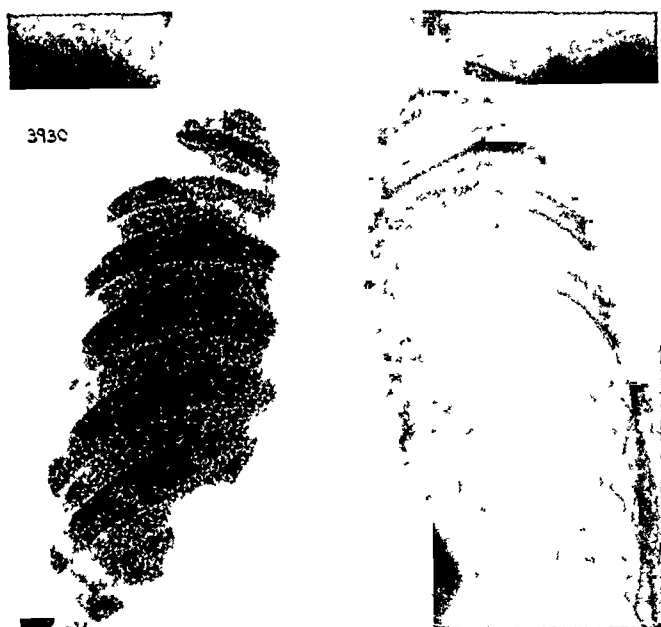


FIG. 12.—Case No. Fbdy. 608. Bone in right bronchus of boy aged twenty years. Probable sojourn eleven years. Note pathology in right lower lobe. Clinical appearances were those of tuberculosis and the patient spent many months in sanatoria for tuberculosis. Bone removed by peroral bronchoscopy, under local anesthesia in five minutes and forty-five seconds. Complete recovery.

Symptoms Due to a Previous Bronchoscopy. As pointed out by H. T. Price,⁹ it is necessary in some cases to distinguish between symptoms due to foreign body in the lung and symptoms due to inexperienced, violent endoscopic or blind attempts at removal. Patients, especially children, often arrive at the Bronchoscopic Clinic with a temperature ranging from 100° to 106° F., some with cough, expectoration, subcutaneous cervical emphysema, pneumothorax, etc., resulting from heavy-handed violent use of endoscopic tubes. These patients or the relatives are told that a few days rest

⁸ Foreign Body in the Lung, Proc. Am. Laryngol. Soc., 1915.

⁹ Clinical Findings of Foreign Body in the Air Passages of Children, Pennsylvania Med. Jour., December, 1915.

are needed between endoscopies; but one cannot escape wonder at the evidence of lack of realization of the delicacy of structure of the air and food passages. Unless pneumothorax, mediastinal emphysema, sepsis or other serious lesions are present the reaction soon subsides with the foreign body still *in situ*, showing that the foreign body was not the cause of the symptoms. A child may be very hoarse and "croupy" from trauma inflicted by the parent's digital attempts at removal of a foreign body that may or may not be or have been present.

DIAGNOSIS OF BRONCHIAL FOREIGN BODY.

The history and mentioned symptoms may indicate clearly the foreign body etiology of the disturbance in the air-passages, but physical and roentgenologic examinations are essential to confirm the inference and to localize the intruder. It is best to study routinely and carefully the physical signs in the chest and to localize the foreign body thereby before roentgenographic studies are made—this even in those cases in which the foreign body is certain to make a clear-cut shadow in the ray plate. By the information thus obtained Spencer has been able to localize with wonderful exactness, as verified when I passed the bronchoscope to remove the foreign body, the non-radiopaque objects whose only shadow, if any, is that of the pathology incident to their presence.

Inspection. If the foreign body has been present for some time a contraction of the chest on the affected side is usually noted. The longer the sojourn of the foreign body the more marked the contraction and asymmetry. In recent arachidic cases, however, it has at times been observed by Spencer¹⁰ that the obstructed side was fuller and that other physical signs and radiographic study by Manges¹¹ revealed more air than on the invaded side, a phenomenon first noted by Iglaue.¹² At the Bronchoscopic Clinic we have come to regard this monolateral emphysema of the obstructed side as diagnostic of peanut-kernels in the lung. The frequency of the occurrence in peanut cases is probably explained by the shape of the peanut-kernel and the fact that the intense localized inflammatory reaction aids in narrowing the lumen. It has seemed to me from observation of foreign bodies as seen bronchoscopically *in situ* before removal that this is not due to a flapping of the foreign body, but rather to the fact that during inspiration the bronchi expand and elongate allowing air to pass on the flat side of the obstructing peanut-kernel, but the shortening and contraction of the bronchi

¹⁰ Jackson, Chevalier, Spencer, William H., and Manges, W. F.: The Diagnosis and Localization of Non-opaque Foreign Bodies in the Bronchi, *Am. Jour. Roentgenol.*, June, 1920, No. 6, vol. vii.

¹¹ *Ibid.*

¹² Three Cases of Foreign Body in the Bronchi, *Lancet-Clinic*, June 1, 1912, No. 22, vol. cii.

during expiration prevent the exit of the air, and, as a consequence, air under pressure is constantly maintained on the obstructed side—an acute obstructive emphysema. This phenomenon is observed, with other objects which set up marked localized inflammation as, for instance, composition buttons and grains of maize. It has also been observed in cases of foreign bodies too small, relatively to the size of the invaded bronchi to cause obstruction solely by bulk. Whether this implies a degree of spasm or not I am unable to say positively. A few cases seemed to show spasm; but the presence of the tube excites spasmodic contraction, which with the alterations of lumen outline associated with the bechic, respiratory and pulsatory movements renders recognition of spasm as a separate entity difficult.

Inspiratory retraction of the interspaces is sometimes observed to be marked on the obstructed side.

Expansion as observed by Thomas McCrae¹³ is more or less limited on the side in which the bronchial foreign body is lodged. It is present even with such small objects as a common straight pin which could obstruct only the smallest bronchi. The limitation of movement becomes more marked as the degree of bronchial obstruction is increased, until with complete obstruction of one lung, respiratory movements are absent on that side.

For the following consideration of physical signs, the author, being unable to present the subject, is indebted to William H. Spencer, who has had the unparalleled opportunity to study the physical signs of all the foreign body cases that came to the Bronchoscopic Clinic in the last three years.

Palpation. Rhoncal fremitus is often of valuable localizing aid. When there exists but partial obstruction in a large bronchus the vibrations are usually most intense posteriorly, over the site of the foreign body. With complete occlusion of a bronchus, however, rhoncal fremitus, if present, will be on the unobstructed side. Vocal fremitus in acute bronchial obstruction is but little if at all altered. With the development of drowned lung and other pathology the tactile appreciation of the voice sounds is diminished.

Percussion. The note obtained in an acute obstruction of a bronchus is of a muffled tympanitic quality—corresponding to the note of a drum which has its air-vent plugged. This curious muffled tympanitic note is most striking in the arachidic cases, in which air under moderate pressure is maintained on the affected side, due to the valve-like action explained under “Inspection,” which allows the entrance but delays the exit of air. As secretions accumulate in the air-passages distal to the obstruction, increasing dulness is found, until over an area of drowned lung the percussion note is flat. With partial obstruction of a bronchus there is always

¹³ The Physical Signs of Foreign Bodies in the Bronchi, AM. JOUR. MED. SC., March, 1920, No. 3, clix, 313.

impairment of resonance distal to the foreign body due to pathologic changes caused by interference with drainage and aëration.

Auscultation. The evidence furnished the ear of the examiner is perhaps the most conclusive part of the examination. The stethoscope correlates the other physical findings and helps us to interpret them correctly. By placing the ear at the open mouth of the patient (not at the chest wall) and requesting a forced expiration one may in certain cases elicit the "asthmatoïd wheeze,"¹⁴ which is a most valuable aid in deciding the presence or absence of a bronchial foreign body which does not show in the radiograph. As the name implies the wheeze has an asthma-like quality, but is dryer and is best heard during a forced expiration after the bronchi have been coughed free from secretion. It may be so loud as to be heard at a distance of several feet or even in the next room. Thomas McCrae listens for it by placing the bell-mouth of the stethoscope at the patient's open mouth. The term "asthmatoïd" refers not to similar etiology or mechanism but to similar sound.

The most constant auscultatory finding is diminished intensity of the respiratory murmur distal to the foreign body. If there be complete occlusion of the bronchus breath sounds are absent below the obstruction. Curiously, vocal resonance is usually but little altered in acute obstruction of a bronchus. Later when "drowned lung" or pulmonary abscess is present the vocal resonance is diminished on the affected side.

The presence and location of rales are of great diagnostic significance. A diffuse tracheobronchitis as seen with organic foreign bodies will be denoted by scattered, loud, snoring, snapping and cracking sounds. These sounds will be most intense on the free side because the presence of the foreign body and the swelling prevents the to-and-fro passage of air on the obstructed side which is necessary to their production. When air can pass an obstruction in the bronchus, rales are formed at this site and can be heard most distinctly posteriorly at the corresponding location on the chest wall. These vibrations are transferred to other parts of the chest, but their greatest intensity is at the point of obstruction.

Occasionally one hears rales of a "tissue-paper" variety over the site of lodgment of a foreign body. These fine crackles and limitation of expansion on one side of the chest were the only physical signs present in a young woman who had aspirated a dental broach while in the dentist's chair (Case No. Fbdy: 683). Vocal resonance like vocal fremitus is usually normal until inflammatory changes or retention of secretion impairs its transmission.

The syndrome of limited expansion, impaired percussion note and absent breath and voice sounds has led many an able observer inexperienced in foreign-body cases to interpret the condition as

¹⁴ Jackson, Chevalier: A New Diagnostic Sign of Foreign Body in Trachea or Bronchi, the "Asthmatoid Wheeze," *AM. JOURN. MED. SC.*, November, 1918, No. 5, xlv, 625.

empyema. Rib resection has been needlessly performed on many patients who afterward came to the Clinic; the pleura, however, had invariably been found to be normal. In many of these cases the foreign-body history had been deliberately ignored by the surgeon, who did not even think it worth while to have a radiograph taken in cases of tacks, nails and other metallic objects.

The characteristic physical signs of an acute bronchial obstruction by a foreign body are limited expansion, muffled tympanitic percussion note and diminished or absent breath sounds on the obstructed side. Vocal resonance and fremitus are but little altered.

Prolonged bronchial obstruction is evidenced by limited expansion, dull or flat percussion note over the base of the lung, diminished or absent breath sounds over that portion of the lung distal to the foreign body and impaired vocal resonance and fremitus. The location of the lesion in the base of the lung should rule out tuberculosis, for tuberculous involvement of the base of one lung is practically never encountered. The presence of the asthmatoïd wheeze is one of the most valuable confirmatory signs; its absence, however, by no means negatives the presence of a foreign body in the bronchus.

Roentgen-ray Examination. After an independent localization by physical signs the foreign body is localized with the fluoroscope and roentgenogram. The best roentgen-ray work is essential. The roentgenologist is given the salient points of the history and the findings and inferences of the examiner of the chest, so that they may work together instead of as separate and sometimes antagonistic units. It is important that both lateral and anteroposterior roentgenograms be made, for an object may not show if it overlay the shadow of the spine, or a flat object, such as a bone lying in the lateral body plane, might be invisible in the anteroposterior view; but the increase in density due to the greater mass through which the rays must pass in the lateral plane in which the foreign body may be edgewise to the rays may cause a definite and clear-cut shadow. At this point it is well to mention the great value of a roentgenogram after the removal of the foreign body, for there may have been two foreign bodies present and but one removed. An instance of this might be cited in which the radiograph showed a coin, but two coins perfectly apposed were removed. Had there occurred a displacement of the approximation of the two coins and but one been removed a continuance of the symptoms would have cast doubt on the operator which would be confirmed beyond explanation by a tardy radiograph, and, worse than all, the patient would have been unrelieved.

Until recently the roentgenologist has depended upon pathologic shadows in the localization of recent bronchial foreign bodies not opaque to the roentgen ray but Willis F. Manges¹⁵ working in

¹⁵ Jackson, Chevalier, Spencer, William H., and Manges, W. F.: The Diagnosis and Localization of Non-opaque Foreign Bodies in the Bronchi, *Am. Jour. Roentgenol.*, June, 1920, No. 6, vol. vii.

conjunction with William H. Spencer on the material coming to the Bronchoscopic Clinic and considering the physical and the ray findings in consultation has been able to demonstrate clearly on the plate certain signs which fully fit the physical findings in these



FIG. 13a.—Case No. Fbdy. 727. Peanut kernel in right main bronchus. Asthmatic wheeze present. Note the depression of the right diaphragm, displacement of heart and mediastinum to the left and increased transparency of the whole right chest.

FIG. 13b.—Note disappearance of the signs two days after removal of peanut kernel from the right main bronchus.

puzzling cases which are mostly of the nut kernel group. These radiographic findings are:

1. Increased transparency on the obstructed side.
2. Displacement of the heart toward the uninvaded side.

3. Downward displacement of the diaphragm and a marked limitation of its motion on the obstructed side. In short, an acute, monolateral obstructive emphysema (Figs. 8 and 13). It is the monolateral character that is especially valuable diagnostically. Bilateral emphysema is less easily detected and is of little significance because it occurs in various conditions. As the obstruction continues accumulation of secretion (drowned lung) and coincident inflammatory reaction make clear-cut shadows distal to the foreign body, rendering the diagnosis easy; but to wait for these signs in arachidic cases might be fatal to the patient. Iglauer¹⁶ was the first to report a case in which the location of a non-opaque foreign body was erroneously interpreted in the radiograph because the foreign body had, by a valve-like action, imprisoned more air in the obstructed side, so that there was shown a very marked emphysema on that side.

The Differential Diagnosis between Tracheal and Esophageal Foreign Bodies is sometimes a point of seeming difficulty to the roentgenologist of limited foreign body experience. The value of a lateral view is here most clear, for one can see the trachea outlined plainly in a well-made plate. Furthermore, it does not seem to be generally known, and therefore it will bear repetition (see *Peroral Endoscopy and Laryngeal Surgery*, p. 226) that disk-shaped foreign bodies seen in the ray to be lying in the sagittal plane must be in the trachea, for they must have entered through the anteroposterior chink of the glottis, and, furthermore, can only remain in that position because the trachea is an open tube with a yielding posterior membranous wall. A disk in order to enter the esophagus must pass flatwise behind the larynx and enter the anteroposteriorly collapsed cervical esophagus in the same position, therefore it will be seen lying in the lateral body plane, usually at the level of the suprasternal notch. A radiopaque mixture can be fluoroscopically seen to pass posterior to the tracheal foreign body, whereas the opaque stream can be seen to divide and pass both anteriorly and posteriorly to an esophageally lodged foreign body.

In order to localize a branch bronchus invaded by a small foreign body the bronchoscopic insufflation of dry bismuth subcarbonate has been of considerable aid.¹⁷ It is not easy to introduce radiopaque substances into the smaller bronchi by injection through the larynx only, for such substances are liable to be promptly coughed out, usually before they reach the carina. By bronchoscopic introduction, however, the opaque substances remain long enough for fluoroscopic and roentgenographic study. A stereoscopic pair of plates will give a beautiful picture of the tree normal or abnormal.

¹⁶ Three Cases of Foreign Body in the Bronchi, *Lancet-Clinic*, June 1, 1912, No. 22, vol. cii.

¹⁷ Jackson, Chevalier: The Bronchial Tree: Its Study by Insufflation of Opaque Substances in the Living, *Proc. Am. Laryngol. Assn.*, 1918; also *Am. Jour. Roentgenol.*, October, 1918.

No toxic or obstructive symptoms have ever been observed to follow the intrabronchial application of the bismuth; radiographic examination showed all of it to have been removed by the ciliary and bechic forces twenty-four hours after its insufflation.

Needles, small headed pins and such objects get very far down and very far out toward the periphery of the lung and into a very small branch bronchus, of which there are many. To search all of these with a probe or minute tube consumes a large amount of time. The positive transparent films of the tracheobronchial tree devised by the author¹⁸ when laid over the negative of the patient will show the foreign body through the transparent tracheobronchial tree and indicate the invaded bronchus. In placing the film, bony landmarks are not reliable because of the wide variation due to the phylogenetic recency of the upright posture. Visceral landmarks are necessary. The two important visceral landmarks are the dome of the pleura and the dome of the diaphragm. Twelve photographic enlargements and reductions are on hand so that a film of the size (rather than the age) is available for any patient, the size being chosen by matching the distance between the dome of the pleura and that of the diaphragm as shown in the radiograph of the patient. To prevent error in the use of these films it is necessary to guard against false localization due to displacement of the lung by atelectasis and especially by compensatory emphysema on the other side.

A negative radiographic report while valuable, if based upon a good plate and given by a roentgenologist of experience, does not exclude the presence of a foreign body, because the thickness of the chest wall, lack of density of the foreign body, faulty technic or inferior roentgenographic apparatus, intractability of the patient or what not may prevent the making of clear-cut plates. The pathology caused by a foreign body will, however, soon make itself manifest and is usually easily recognized in the roentgenogram. As before mentioned, however, to wait for these signs to appear might be of serious consequence to the patient. If the history, symptoms and physical signs are present we must therefore disregard the negative ray findings and proceed with the endoscopic search for the foreign body.

FOREIGN BODY IN THE PHARYNX.

Fish bones are perhaps the most frequent of pharyngeal foreign bodies, and they, as do other thin, sharp objects, lodge most frequently in the crypts of the faucial or lingual tonsillar masses. The subjective localization of the object by the patient is usually rather vague, although the side on which the object lies can usually be designated. Pain of a "sticking" character is the usual complaint with pointed objects. Swallowing increases the discomfort,

¹⁸ *Peroral Endoscopy and Laryngeal Surgery*, text-book, 1914.

and because of this the patient often refrains from eating. In his student days the author himself had a bone of a reed-bird lodge on the posterior surface of his left tonsil. It was not visible on inspection, but was found by Charles E. de M. Sajous by palpation with the index finger and removed digitally. Large foreign bodies such as tooth plates, boluses of meat and even live fish have been known to suffocate the patient. This is so well known that students are taught in their course in internal medicine to search the pharynx for foreign objects in all cases of coma. A foreign body may be coughed from the lower air passages into the nasopharynx and be overlooked for some time unless this possibility be considered.

If the object be lodged near the larynx, violent coughing may result. Vomiting and retching often occur early but cease rather soon. Examination should show the foreign body, but rather close scrutiny may be necessary to find a small fish bone. Blind efforts at removal are never justified and much mutilation can be done by groping about with forceps and fingers. Culp¹⁹ reports the interesting case of the removal, from the sublingual sinus near its attachment to the epiglottis, of a needle which was said by the patient to have entered the left knee eleven years before while she was scrubbing the floor. In the literature there are reports of a number of cases of wandering foreign bodies that have been removed from remote tissues years after entrance from the food passages, but none from the air-passages proper.

In the diagnosis of a foreign body in the pharynx the following points are worth remembering: Pharyngeal foreign bodies are usually readily located by the patient from subjective sensation and by direct inspection by the surgeon. Thin, sharp objects usually lodge in the tonsillar masses. The possibility of lodgment in the nasopharynx must be kept in mind. The roentgen ray, inspection and palpation are the most important means of diagnosis. The roentgen-ray work must be done by an expert with the very best equipment; inspection requires good illumination with head mirror or head lamp and laryngeal and postnasal mirrors to look "around the corner," back of the tongue, tonsils, pillars, velum, etc. Palpation by the index finger is essential when other means are negative, but the palpation must be gentle and the surgeon must be familiar with the feeling of the various structures. The author has seen cases in which one cornu of the hyoid bone was felt and denuded in blind attempts at forceps removal of a supposed bone for which the cornu of the hyoid bone was mistaken.

FOREIGN BODY IN THE ESOPHAGUS.

Dysphagia, Odynophagia and Subjective Sensation of a Foreign Body. Dysphagia is the most prominent symptom of esophageal

foreign bodies, varying in degree with the size of the intruder, the degree of spasm and inflammatory reaction it induces. Complete obstruction is most often seen when a meat bolus becomes impacted at the mouth of the esophagus. A very small foreign body may cause regurgitation and complete inability to swallow even water. This *complete occlusion* may be due to spasm, swelling of the esophageal walls, augmentation of the size of the foreign body by expansion with absorbed moisture or by accumulation of food about the intruder. Coins may cause intermittent occlusion by tilting. Intermittent occlusion may also be due to lodgment of food above the intruder. On the other hand a foreign body of long sojourn may cause no appreciable dysphagia. The subjective sensation of foreign body and of obstruction is commonly present, although in children it may be overlooked. In some cases the localization of the patient is correct, in other cases the sensation may be reflected from the present location or may be the site of a previous location. Sharp, foreign bodies at the hiatus are often felt by the patient in the neighborhood of the ensiform cartilage. Pain is present when large objects are impacted or when pointed foreign bodies penetrate the walls of the esophagus. When cervical periesophageal inflammation exists there is usually marked tenderness and pain on swallowing. Substernal aching is not an infrequent complaint when objects are lodged in the thoracic esophagus and painful spasm at the hiatus may be caused by a foreign body or an erosion produced thereby. Pain and the subjective sensation of foreign body are, however, not dependable signs of the actual presence of a foreign body if there does not exist a coincident dysphagia; and it must be remembered that difficulty in swallowing may be imaginary. Abrasions and inflammation caused by the temporary lodgment of a foreign body in the esophagus may create and maintain the pain, subjective foreign body sensation and even dysphagia for a time after the passage of the object. These symptoms subside in a short time and will be greatly relieved by the administration of bismuth subnitrate, preferably with calomel for the first few doses, dry on the tongue, for its protective and slightly antiseptic action.

Excessive Salivation usually accompanies complete occlusion of the esophagus by a foreign body and is very distressing, causing drooling or constant expectoration, and cough by overflow into the larynx.

Dyspnea may be a symptom of an esophageal foreign body which because of its size produces compression of the trachea, or of a pharyngeal foreign body overhanging the larynx. It is well to bear in mind that dyspnea and hoarseness may be present from previous attempts at removal by parents or practitioners. Many such cases have come to the clinic, some of them without any foreign body being present. *Cough* is an important symptom in some esophageal cases and may be due to overflow of secretions into the larynx, or to

perforation, traumatic or ulcerative, of the party wall, allowing leakage of food or secretions into the trachea. In a few instances it has seemed to be of reflex origin.

Hematemesis and Hemoptysis are not uncommon, and if the foreign body penetrate a large vessel fatal hemorrhage may result.

Wry-neck. Holding the head on one side we have noticed in a number of cases coming to the clinic usually in very young children. In one such instance a boy was sent to F. F. Borzell for suspected disease of the shoulder-joint. Borzell fluoroscopically found a coin in the esophagus.



FIG. 14.—Case No. Fbdy. 695. Open safety-pin in the esophagus regurgitated after a seven weeks' sojourn in the stomach. Pointed shaft buried in the anterior wall of the esophagus up to the spring. Point directed toward the pericardium. Child admitted, with temperature of 106° . Complete recovery after esophagoscopy removal.

Fever is often present in children. One very interesting case (Case No. Fbdy. 695, Fig. 14) was that of a child of nine months who had swallowed an open safety-pin which had remained in the stomach two months and was then regurgitated into the esophagus. The point had penetrated the esophageal wall and was pointing toward the pericardium. The patient was extremely toxic and had a temperature of 106° . The temperature fell immediately on removal of the pin, showing that it had been the cause of the disturbance. Recovery was prompt and complete.

Roentgenography and Fluoroscopy. If the object be radiopaque it will readily be seen in the fluoroscopic study and on the radio-

graph. Anteroposterior and lateral studies should be made. Roentgenograms often show foreign bodies invisible in the fluoroscope. A small plate low down on the neck close to the clavicle often shows a foreign body invisible in the anterioposterior plate. If the foreign body be not of sufficient density to show with the roentgen ray the point of obstruction can be demonstrated fluoroscopically by having the patient swallow some barium mixture or, better still, by watching the progress of a barium-filled capsule, as urged by Ellen J. Patterson. The capsule will lodge at the site of lodgment of the foreign body and on slowly dissolving may outline the intruder. It is necessary for the fluoroscopist to be familiar with the hesitations often seen in cases with a perfectly normal esophagus. Interpretation of the radiograph must be by the roentgenologist, and none but the very best plates are of any value negatively. Over and over again foreign bodies have been found in good plates after negative opinions had been given, prior to admission, on the basis of poor plates. The most common site of lodgment is at the superior aperture of the thorax, where flat objects are seen lying in the lateral plane of the body. Once dislodged from this location foreign bodies are liable to go downward into the stomach provided they are not too large to pass through the hiatus esophageus. It has been our observation that if a foreign body passes unaided through the hiatus it will usually go through the pylorus and be expelled per rectum. For localization it is sometimes necessary to insufflate bismuth subcarbonate into the bronchi so they will cast a shadow.²⁰

Symptoms Due to Attempts at Removal of Esophageally-lodged Foreign Bodies must be differentiated from symptoms due to the intruder itself. This is of the utmost importance because, if the symptoms are due to the foreign body, as in the case of the safety-pin above mentioned, immediate removal is imperatively demanded to save the patient's life. In such cases there is little or no hope that the symptoms will subside until the intruder is removed, and the sooner it is taken out the better. On the other hand, traumatic esophagitis due to blind bouginage or inexperienced, violent or prolonged esophagoscopy, is a dangerous condition, the cure of which, if curable at all, depends on rest and quiet, with bismuth and calomel dry on the tongue, fluid diet, etc. To esophagoscope a lacerated inflamed edematous esophagus in search of a foreign body is to court both failure and disaster. The usual symptoms of traumatic esophagitis are dysphagia, odynophagia, cervical tenderness, cervical subcutaneous emphysema most often discoverable by palpation on or near the inner end of the clavicle, foul breath, anorexia and fever. Children are often brought to the Bronchoscopic Clinic in this condition, and it is necessary to explain to the parents

²⁰ Jackson, Chevalier: *The Bronchial Tree: Its Study by the Insufflation of Opaque Substances*, Am. Jour. Roentgenology, October, 1918, v, 454.

that an interval is advisable between esophagoscopies. In one case D. R. Bowen noted the barium mixture dividing into a number of streams, which phenomenon was found at esophagoscopy to be due

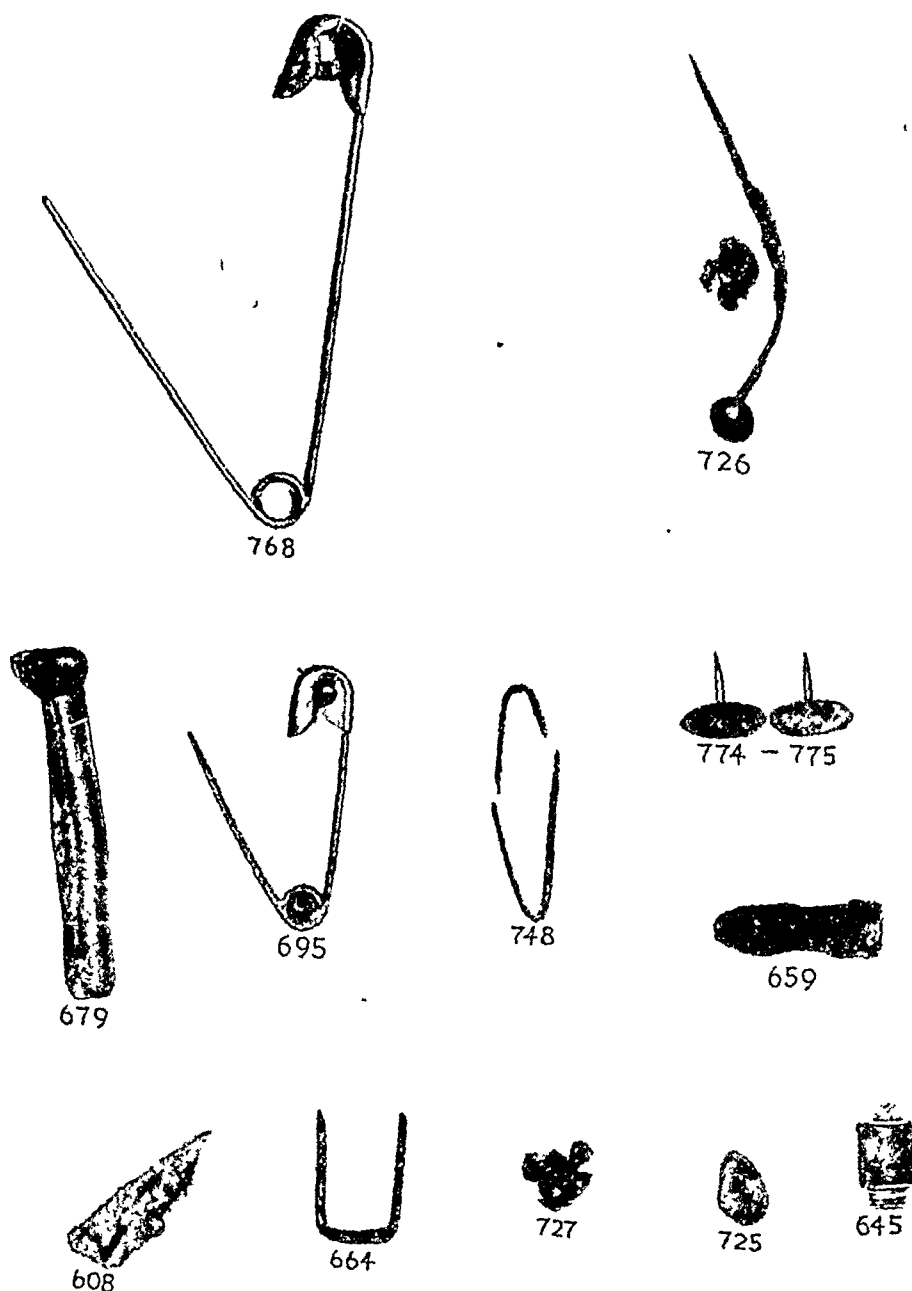


FIG. 15.—Foreign bodies removed from the air and food passages by endoscopy through the mouth in the cases shown in the preceding roentgenograms. Illustrations are actual size.

to masses of edematous mucosa looking like sessile nasal polypi and they had undoubtedly resulted from the violent prolonged inexperienced esophagoscopy done before admission. "Don't use blind instrumentation or bouginage!" should be the first words of the diagnostic discussion. The former very high mortality of esophageal foreign bodies can be attributed to the methods employed for their diagnosis and removal. Esophagoscopy has revolutionized the treatment and minimized the mortality of removal while the roentgen ray renders bouginage for diagnosis not only unnecessary but reprehensible.

SUMMARY OF THE CHIEF POINTS IN THE SYMPTOMATOLOGY AND DIAGNOSIS OF FOREIGN BODY IN THE AIR AND FOOD PASSAGES.

Larynx.

1. Foreign bodies lodged in the larynx cause an initial laryngeal spasm which is followed by more or less laryngeal wheezing, croupy cough, and a variable degree of impairment of phonation.

2. Pain in the laryngeal region may be present and is sometimes referred to the ears.

3. The larynx may tolerate a thin, flat foreign body for a relatively long period of time, but the development of increasing dyspnea renders early removal imperative in the majority of cases.

Trachea.

4. Tracheal foreign bodies are usually movable and their movements can usually be felt by the patient.

5. The vibrations may be palpated and heard with the stethoscope.

6. Cough is usually present at once, may disappear for a time and recur, or may be continuous, and may be so violent as to induce vomiting.

7. Sudden shutting off of the expiratory blast and phonation during paroxysmal cough is almost pathognomonic of a movable tracheal foreign body.

8. Dyspnea is usually present and is due to the bulk of the foreign body plus the subglottic swelling caused by the traumatism of the shiftings of the intruder.

9. The asthmatoïd wheeze is usually present and is often louder and of lower pitch than the asthmatoïd wheeze of bronchial foreign bodies. It is heard at the mouth, not at the chest wall.

10. Pain is not a common symptom, but may occur and be accurately localized by the patient.

EARLY SYMPTOMS OF IRRITATING FOREIGN BODY (SUCH AS A PEANUT-KERNEL) IN THE BRONCHUS.

Bronchi.

11. Initial laryngeal spasm is almost invariably present with foreign bodies of organic nature such as nut kernels, peas, beans, maize, etc.

12. A diffuse purulent laryngo-tracheo-bronchitis develops within twenty-four hours in children under two years.

13. Fever, toxemia, cyanosis, dyspnea and paroxysmal cough are promptly shown.

14. The child is unable to cough up the thick mucilaginous pus through the swollen larynx and may "drown in its own secretions" unless the offender be removed.

15. Lung abscess rapidly forms.

16. The older the child the less severe the reaction.

17. In the early stages an acute obstructive emphysema is present, manifested by: (a) Limited expansion, (b) muffled tympanitic percussion note, (c) markedly diminished or absent breath sounds on the obstructed side, (d) many rales and harsh breathing on the free side.

18. The radiograph confirms these signs by showing (a) greater transparency on the obstructed side, (b) displacement of the heart toward the free side, (c) depression and limitation of the diaphragmatic movement on the obstructed side.

SYMPTOMS OF PROLONGED FOREIGN BODY SOJOURN.

Bronchi.

19. The time of inhalation of a foreign body may be unknown or forgotten.

20. Cough and purulent expectoration ultimately result although there may be a protracted delusive symptomless interval.

21. Periodic attacks of fever, with chills and sweats and followed by increased coughing and the expulsion of a large amount of purulent, usually more or less foul material are so nearly diagnostic of foreign body as to call for exclusion of this probability with the utmost care.

22. Emaciation, clubbing of the fingers and toes, night-sweats, hemoptysis, in fact all of the symptoms of tuberculosis are in most cases simulated with exactitude, even to the gain in weight by an outdoor regimen.

23. Tubercle bacilli have never been found in the Bronchoscopic Clinic associated with foreign body in the bronchus. It was the only element lacking in a complete clinical picture of advanced tuber-

culosis. A point of difference was the rapid recovery after removal of the foreign body.

24. The erroneous statement in all of the text-books that foreign body is followed by phthisis pulmonalis is an heirloom of the days when the bacillary origin of true tuberculosis was unknown, hence the foreign body phthisis pulmonalis or pseudotuberculosis was confused with the true pulmonary tuberculosis of bacillary origin.

25. The subjective sensation of pain may allow the patient to localize a foreign body accurately.

26. Foreign bodies of metallic or organic nature may cause their peculiar taste in the sputum.

27. Offensive odored sputum should always suggest bronchial foreign body; but absence of sputum, odorous or not, should not exclude foreign body.

28. Sudden complete obstruction of one main bronchus does not cause noticeable dyspnea provided its fellow is functioning.

29. Complete obstruction of a bronchus is followed by rapid onset of symptoms.

30. The pleura is rarely involved. Rib resection done for supposed empyema have with one exception shown no pus.

31. The physical signs usually show limitation of expansion on the affected side, impairment of percussion, and lessened transmission or absence of breath sounds distal to the foreign body.

32. The "asthmatoïd wheeze" may, if present, be of great diagnostic value. Its absence, however, does not negative the presence of foreign body.

33. All cases of chest disease should have the benefit of a radiographic study to exclude bronchial foreign body as an etiological factor, and negative opinions should never be based upon any plates except those of the utmost perfection that the wonderful modern development of the art and science of roentgenology can produce. In doubtful cases, the negative opinion should not be conclusive until a roentgenologist of long and special experience in chest work has been called in consultation. Even then there will be an occasional case calling for diagnostic bronchoscopy.

34. Symptoms of pulmonary abscess, or other lung disease, even cough, following within a few weeks of the extraction of teeth, call for the exclusion of foreign body in the lung.

Esophagus.

35. There are no absolutely diagnostic symptoms of esophageal foreign body.

36. Dysphagia, however, is the most constant complaint, varying in degree with the size of the foreign body and the degree of inflammatory or spasmodic reaction produced.

37. Pain may be caused by the penetration of a sharp foreign body, by inflammation secondary thereto, by impaction of a large object or by spasmodic closure of the hiatal sphincter.

38. The subjective sensation of foreign body is usually present but cannot be relied upon as assuring the presence of a foreign body for it is present for a time after the passage of the intruder.

39. All of these symptoms may exist, often in most intense degree, from previous violent attempts at removal and the foreign body may or may not be present.

40. Fluoroscopic study of the swallowing function with barium mixture or capsule will give the location of a foreign body which may not be radiopaque.

41. Anteroposterior and lateral roentgenograms should always be made.

42. The value of a radiograph after the removal of the foreign body cannot be too strongly emphasized.

Stomach.

Foreign body in the stomach ordinarily produces no symptoms. The roentgenogram and the fluoroscopic study with an opaque mixture are the chief means of diagnosis.

CANCER OF THE UTERUS.¹

BY JOHN B. DEAVER, M.D.,

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WITH A DESCRIPTION OF THE PATHOLOGY.

BY STANLEY P. REIMANN, M.D.,

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VERY often it must seem as though the pursuit of the cancer problem were like chasing the elusive will o' the wisp. But the vocabulary of the scientists contains no such word as fail, and surely some day the solution will be at hand. It may burst upon us from some hitherto unsuspected source, but it is sure to come, for it is inconceivable that all the investigations that are devoted to this subject should be fruitless. Without an exact knowledge of the causative factor of cancer we cannot, of course, expect to prevent its development; but until that time arrives no means of mitigating its evil should be untried. There are not a few indications that the

¹ Read before the Southern Surgical Association, Hot Springs, Va., December 15, 1920.

surgeon may be asked to lay down his knife as far as cancer, more especially cancer of the uterus, is concerned and make room for radiotherapy, either roentgen ray or radium, or what seems the most satisfactory method, a combination of the two.

One of our English colleagues in discussing these methods in the treatment of uterine fibroma laconically remarks, "When the pen has superseded the sword the scalpel will still be needed for myoma." I believe this also applies to cancer of the uterus in spite of the very gratifying reports concerning the non-operative treatment of these cases.

As in all types of disease the demand for early recognition of cancer and of precancerous changes is imperative. But we are confronted with the question, is early diagnosis possible? If the answer to this question cannot be definitely positive it can at least be said that certain clinical phenomena are suggestive and sufficiently so to command attention. Among such suggestive clinical signs may be mentioned intermenstrual bleeding, increase in quantity, duration and periodicity of the menstrual period in the active uterus, especially at the onset of the menopause, and a bloody discharge after the latter has been established. The character of bleeding between periods may vary from a slight discharge from what might be termed hemorrhage, and is usually excited by irritation, as during urination, defecation or by examination or manipulation. The latter particularly should arouse suspicion, as it is in all probability due to erosion of capillary vessels influenced by the tumor cells.

The character of the vaginal discharge is also suggestive. In the incipient stage of cancer it may differ from the normal only in amount or it may be serosanguineous, but it is usually in a later stage that it becomes distinctly blood-stained while in the advanced stage it is purulent and foul-smelling.

As in nearly all forms of internal cancer, pain is, unfortunately, not an early symptom of uterine cancer. Indeed, owing as much as anything to the poor supply of sensitive nerves in the cervix and the body of the uterus, pain is an indication of infiltration beyond the uterine limits and is thus a most discouraging sign. But, as I have said, these signs are merely suggestive—diagnosis must rest on careful inspection and digital and microscopic examination. The latter is of the utmost importance. That is to say, careful examination of the products of curettage or an excised portion of the cervix is of immeasurable value as a diagnostic aid in detecting carcinoma that might otherwise be overlooked. If only one case in a hundred thus examined prove positive for carcinoma the procedure is justified. Curettage should include the body and fundus as well as the cervix. The predominance of cancer in the cervical portion of the uterus is well known. This fact is of importance in the association of carcinoma and fibromyoma. For this reason chiefly,

and also to prevent an obstinate future vaginal discharge, it is my practice in all cases of fibromyoma of the uterus approaching the menopause, in the menopause or after the menopause to do a complete removal. Statistics show that 2 or 3 per cent. of myoma uteri are associated with carcinoma of the cervix. It is readily seen that in precisely that proportion of cases the examination of cervical scrapings with positive results will indicate a total hysterectomy where otherwise a subtotal operation might have been done, thus contributing to the list of cases of cancer of the cervix developing after a supravaginal hysterectomy.

Curettement, however, has its serious limitations, inasmuch as material taken from one portion of the uterus may be entirely free from suspicion while malignancy may possibly be lurking in another part. In view of this it seems to me that the more rational method of obtaining information would be by direct inspection by means of a hysterotomy, a method which I have advocated on many occasions and practised with entire satisfaction. It is an open method, and in this consists its greatest advantage.

It is perhaps a fortunate thing, from a diagnostic standpoint, that the cervix is the more common site of uterine carcinoma, and it is important in this connection that in this location it spreads very rapidly, causes earlier fixation of the uterus and extension into the broad ligaments and walls of the vagina. Of value also is the fact that carcinoma of the cervix in the vast majority of cases develops in women who have had children. Very often there is present a laceration not entirely healed and presenting a reddened, eroded surface covered with a discharge and giving evidence of chronic inflammation. The pathologist sees in these cervixes ulceration of the mucosa, irregularities in the epithelium covering the edges of these erosions, dense, scar tissue distorting and ensnaring epithelial cells piled on the lining, cystic dilatation of the glands with distortion of the lining epithelium and the like. It is not at all unusual for me to receive pathological reports which read: "Cannot tell whether this is carcinoma or not, but it may be." In such instances I do not hesitate a moment about removing the uterus. Curettage or any other time-wasting procedure has no place here. Certainly, I also remove a portion of the cervix for microscopic study.

The pathological changes that lead to cancer of the body and the fundus of the uterus are not so clear. But there are certain evidences of glandular hypertrophy, excessive secretion and desquamation with subsequent hyperplasia of lining cells which are, to say the least, suggestive of precancerous conditions.

When I do a hysterotomy I notice, of course, great shagginess, ulceration, fragile hemorrhagic endometrium, but also on the line of incision or any suspicious looking area I look for a sharp line of demarcation between endometrium and musculature. Very often normally there are a few glands beyond the line of the endometrium,

but in general the dividing line is fairly sharp. Whenever I see tissue like endometrium invading the musculature I am suspicious and do not hesitate to give the patient the benefit of the doubt.

In the presence of undoubted cancer, complete hysterectomy is probably as sure a means of curing the disease as we have, provided, of course, that the growth is not so far advanced as to threaten adjacent tissues. It is these cases also that the radiologist believes are the most amenable to their treatment. This may be so, but it has not been my experience. I have too often seen an apparent regression of the tumor for several months after radium treatment, only then to be confronted with evidence of recurrence. This may possibly be due to faulty technic, but the same holds good, to a large extent, with regard to surgical failures. There is, however, less excuse for the latter, since the technic of the operation enjoys a certain degree of perfection, although at the same time it requires skill and experience. Radiotherapy, on the other hand, may be said to be still in its formative period, but its technic is probably more easily acquired. The gist of the matter no doubt is that the tyro in either method helps to discredit the one as he does the other.

Unfortunately the surgeon so frequently sees the baneful effects of radiotherapy in cases that were either mishandled or unsuitable for the treatment that it is only natural that he should not sing its praises in loud tones. Not long ago I had occasion to operate upon a woman who, under a diagnosis of cancer of the uterus, had been treated elsewhere with radium, the dosage and time of exposure of which I do not know. She was brought to the Lankenau Hospital with evidence of peritonitis and an abscess in the cul-de-sac. I drained the abscess and did a hysterectomy. The woman died two months later following a stormy, septic course. Autopsy showed sloughing masses in the sigmoid, perforations, etc. No evidence whatever of carcinoma could be found in spite of the most painstaking search and section study of the uterus. The pathological diagnosis consisted of a small subserous myoma. This, of course, is a case of mistaken diagnosis and in no way reflects on the efficiency of radium, but it does illustrate the dangers of its use in inexperienced hands.

On the other hand the pathologist of the Lankenau Hospital, Dr. Stanley P. Reimann, has made a study of uteri removed, surgically, from one to five weeks after treatment with radiation. Of two particular cases the one, a squamous-cell carcinoma of the cervix, showed great destruction of carcinoma cells with intense congestion and polymorphonuclear and other cell infiltration. The destructive effect was seen throughout the length of the cervical canal and extending about $1\frac{1}{2}$ cm. into the wall, but *beyond this were numerous living carcinoma cells.*

In the other case, which clinically presented continuous small

hemorrhages and aroused the suspicion of carcinoma of the fundus of the uterus, the uterus was soft and boggy, the entire uterine cavity giving evidence of intense inflammatory reaction, the mucosa and considerable muscle tissue immediately about the site of the radium being necrotic and deeply ulcerated. The remainder of the mucosa also showed ulceration extending from a part to a whole of this structure. Beyond the necrotic area here, likewise, there were living carcinoma cells.

My remarks have been made on the basis of 500 hysterectomies performed by me at the Lankenau Hospital since January 1, 1916. These 500 cases comprise carcinoma of the uterus, 27 (no deaths); myoma uteri, 367; diseases of the uterus, tubes and ovaries, 106, among the last being 6 ovarian cysts associated with malignancy. The operative mortality of the entire series was 2 per cent., 10 deaths. The details appear in the table given below.

In conclusion, I would say that there is no gainsaying the fact that for certain well-selected cases, more especially inoperable ones, radiotherapy has a tremendous field of usefulness. If the day is at hand when it can be judiciously and successfully applied to all cases of cancer, none would more eagerly hasten the time than the surgeons themselves. The object of the profession at all times is to mitigate and to rid the world of cancer, one of its most distressing sore spots.

	Number.	Deaths.
Myoma uteri	367	6
Chronic cervicitis	10	
Chronic endometritis	32	3
Salpingo-oöphoritis	18	
Prolapse, uterus	20	
Prolapse, vagina	2	
Vesicovaginal fistula	2	
Ectopic pregnancy, left cornu	1	
Bicornuate uterus with chronic endometritis	1	
Ovarian cyst (malignant, 6)	14	
Acute suppurative endometritis	5	1
Hydatidiform mole	1	
Carcinoma of the uterus	27	
Cervix	11	
Fundus	12	
Chorio-epithelioma	2	
Carcinomatous polyp	2	
	<hr/> 500	<hr/> 10

MULTIPLE SCLEROSIS AND PSYCHOANALYSIS.*

A PRELIMINARY STATEMENT OF A TENTATIVE RESEARCH.

BY SMITH ELY JELLIFFE, M.D., PH.D.,

NEW YORK.

My personal interest in what has been subsumed under the term "multiple sclerosis" began in 1900. At that time, working in the Vanderbilt Clinic with A. B. Bonar, some 60 cases were examined in great detail from the sensorimotor point of view, and a monograph on the disease was projected, the first approach toward which was published by one of us in 1904. This short study appeared as an inquiry into the then thought of etiologic factors and analyzed the general features in over 100 observations.¹ The necropsy material was quite limited, however, the patients having been drawn from polyclinic material, and when Müller's² excellent monograph appeared in this same year, documented on rich necropsy material, the rather ambitious program that had been drawn up was abandoned as projected.

Since that time, however, my collecting propensities have always maintained a special predilection for this interesting syndrome. I have become more or less sensitized to the problems involved. They have never been far from the focus of my interest and the many perplexities and difficulties have been the subject of much inquiry from clinical sources, the chemical laboratory, pathologic section and therapeutic endeavor.

So far as the pathologic pictures have contributed to the furthering of the little knowledge that we as yet possess, without burdening this short *resume* with too exhaustive an analysis, it has been learned definitely that disseminated foci, which may occur in the cerebro-spinal pathways and arise from a variety of causes, may produce clinical pictures which on cross-section have many features that would entitle them to be diagnosed as "multiple sclerosis." These may be termed, for the purpose of this note, the *secondary types*, with the discussions concerning which this Society is fairly familiar. Certain cases of infection from a variety of organisms (influenza, poliomyelitis, lethargic encephalitis) and a special group of disseminated syphilitic encephalomyelitides offer especially interesting polemic material, attention to which has been called by a number of observers, notably Riese,³ Schülze,⁴ Klingman⁵ and Spiller.⁶

* Presented before the American Neurological Association, June, 1920.

¹ Jelliffe, S. E.: Multiple Sclerosis: Etiology, Jour. Nerv. and Ment. Dis., July 1, 1904.

² Die multiple Sklerose des Gehirns und Rückenmarks, Jena, 1904.

³ Arch. f. Psychiat., 1919, vol. lx.

⁴ Deutsch. Ztschr. f. Nervh., 1920, lxx, 1.

⁵ Am. Arch. Neurol. and Psychiat., 1919, i, 39, 193.

Ibid., 1919, i, 219.

The new spirochete of Kühn and Steiner may be included here if finally verified. With these secondary types, mostly of infectious origin, however, we are not now concerned.

More and more it has come to be believed that a special type with a fairly distinctive pathologic foundation is recognizable. Many, perhaps most, of the so-called *primary multiple sclerosis* are to be thought of in this connection, but neuropathology is not yet in a position to decide offhand even concerning this point.

The pathologic picture of what I take to be this group has been most exhaustively analyzed by Dawson,⁷ Klingman and others, and it is with reference to this hypothetical series of cases that the present series of notes applies.

Here the chief pathological lesion seems to have its inception in a special type of disturbance of the vascular apparatus which is functionally integrated with the work being carried on in the different neural metameres. The minute histology of these changes I shall not discuss here. Klingman, Dawson, Cassirer and others have afforded the details for the conception. I simply wish to call attention to certain affiliations with another type of vascular alteration in which the detail of the histological picture is closely related, if not identical.

Even should it require an extensive polemic to decide concerning the identity of these changes the point at issue is not seriously modified. These changes are those lying behind what has been called the exudative diathesis and of which the studies of Cassirer⁸ have given us a broad outline. The catatonic "Hirnschwellung" of Rieger and Reichardt⁹ is one of the manifestations of this type of vascular dysfunction upon which special emphasis may be laid as well as to various so-called neurotic arthritides, skin exudates, asthmatic exudates, hay fever, etc. The relationship of these phenomena to the vegetative nervous system control and attendant psychological factors is the concept which is of interest in this research and which has a large and important background. This general background has been elaborated *in extenso* and made the basis of an attempt at a unified attack upon the whole problem of nervous diseases and a general dynamic pathology as well.¹⁰

Shifting for a moment now to physiological considerations, attention should be called to the generalization of what Sherrington¹¹

⁷ The Histology of Disseminated Sclerosis, Rev. Neurol. and Psychiat., 1916, xiv, 285; Tr. Royal Soc., Edinburgh, 1916, pt. 3, No. 18, i, 517 (with complete bibliography).

⁸ Die vasomotorisch-tropischen Neurosen, ed. 2, Berlin, Karger, 1912.

⁹ Ueber "Hirnschwellung," Ztschr. f. d. ges. Neurol. u. Psychiat., 1911, iii, 1.

¹⁰ See introduction to text of Jelliffe and White: Diseases of the Nervous System, 1919, 3d ed. Also see Brown, W. L.: Sympathetic Nervous System in Disease, 1920. Kempf: Autonomic System and Personality; Nervous and Mental Disease Monograph Series, 1919. Noel Paton: Nervous Regulators of Metabolism, 1919. White: Foundations of Psychiatry, Nervous and Mental Disease Monograph Series, No. 32.

¹¹ Integrative Action of the Nervous System, New York, 1906. Also see Childs: Evolution of the Nervous System, Chicago, 1920.

first termed the "action pattern." I need hardly refer to the automatic integrating work which is constantly going on in response to conscious and unconscious desires, to the complicated series of neural, vascular and biochemic integrations which, under the organization of the vegetative nervous system, are in constant working activity, carrying on the biologic work of satisfying necessary human cravings, the satisfaction of which means the maintenance of the individual and the continuance of the phylum.

It was at this point some five years ago that I determined to learn, if possible, from the study of the unconscious thought processes, whether any information could be obtained whereby one could predicate whether something was amiss with the unconscious action patterns, and if so whether any correlations could be made between such faulty action patterns and the neurovascular integrations that would be called on in the attempt to carry these action patterns out or to control the resultant behavior.

Up to the present, then, the argument briefly stated is that in a certain type of "multiple sclerosis" patients, certain vascular reactions occur which permit exudative and proliferative changes of a nature similar to those seen in certain exudative constitutional states known to be intimately related to vegetative nervous system disorders of a special type.

These foci are disseminated and follow no as yet understandable principle of localization. We assume, however, that the locus of distribution is in some way related to an action pattern of some kind. That the neural integrative mechanisms needed to carry out the action pattern is under a chronic state of postural tonus and that the vascular integration mechanisms which are required to supply the neural metamere to carry out the action pattern is under a particular and special form of stress.

The vascular alterations are known to be closely bound up with emotional stimuli. Hence the problem postulated is to ascertain if there are specific emotional stresses going on in the unconscious which may be correlated with the rest of the mechanisms here outlined.

For example, suppose the initial symptoms of a multiple sclerosis were those of a choroiditis with eye-muscle unbalance; then that these were followed some few years later by pyramidal tract symptoms chiefly involving the long flexors of the thigh and the extensors of the leg of the right side, making the movements of getting into an erect posture, going up stairs, kicking, etc., difficult. Now an investigation of the proprioceptive nerve supply of the ocular muscles involved in the unbalance and the postural tonus of these muscles as they pull upon the eyeball is imperative. What relation could a chronic pull from possibly unconscious activities have upon the vegetative control of the metabolic elements of the sclera, the choroid and possibly by extension to the retina? The pathologic

picture here needs investigation. So far as I can find it never has been done. What part does the retina play in this unconscious fixation?

Then as for the muscle groups involved in the pyramidal tract impairments. The character of the defect tends to point to certain localizations in or about the chief integrating pathways to permit certain types of action. What is this action pattern? Are there chronic postural tonicities under constant unconscious emotional stimuli that may impair the metabolism of the reflex vegetative arcs involved in the action patterns? If so, how are such unconscious emotional strivings to be recognized, evaluated and finally correlated with the rest of the situation?¹² Such is a partial statement of the bare outlines of the problem.

The details and the significance of the work of Pavloff, Cannon,¹³ Kempf¹⁴ and others working in this newly opened field I shall assume is known to all here present—even the polemic material concerning the validity of the generalizations that definite and predicable changes in the entire physiologic activities as well as morphologic alterations of the cells of the body may be occasioned by emotional reactions, such as hunger, fear, rage, pain, etc., I shall also assume you to be thoroughly acquainted with. I need not go over the arguments. They are obvious.

What the early studies of these investigators proved was that certain correlations proving the general validity of the position here taken are capable of being experimentally repeatable and verifiable in lower animals. The vast literature of psychiatry shows that similar correlations, though more intricate, are true for human beings.

My material is necessarily limited. It has been difficult at times to get the necessary coöperation. Either the patients were not suited for the studies which I hoped to make, because of the mental deterioration so frequently observed in multiple sclerosis, or they lacked the time, or they were not sufficiently intelligent to enter into the investigations in any hopeful sense.

My material in this experimental research is drawn from five patients, only two of whom offered some approach to helpful coöperation. The most fruitful material was obtained from these two patients who could continue psychoanalytic procedure for several months.¹⁵

¹² Sherrington: *Proprioceptive Nerve Supply of Ocular Muscles*, Brain, 1918, li, 332. *Postural Activity of Muscle and Nerve*, Brain, 1915, xxxviii, 101. Kempf, loc. cit.

¹³ *Fear, Rage, Hunger and Pain and the Nervous System*, New York: D. Appleton & Co., 1919.

¹⁴ *The Autonomic System and the Personality*, Nerv. and Ment. Dis., Monogr. Ser. 28, New York and Washington, 1919. *Psychopathology*, St. Louis, 1920.

¹⁵ Jelliffe: *Technic of Psychoanalysis*, Nerv. and Ment. Dis., Monogr. Ser. 26, New York and Washington, 2d ed., 1920.

What developed? In the first place there was an extremely interesting uniformity in the character of the dream material:

1. All of the patients gave me very definite archaic symbolizations.¹⁶ We are scarcely able yet to go far into this nor into the as yet incomplete generalizations as to the significance of this material as bearing on the thwartings of the cravings of the patients and the influence of these thwarting on the neural mechanisms of the action patterns and of the metabolic upkeep.

Yet we must consider to some extent such things as these definite archaic symbols, since they may have a special significance in our measurement of the affective disturbances contributing to the patient's illness. Any therapeutic measure must be based on some notions of exactness. I think it was Plato who was among the earliest to insist on the value of the reduction to measurements in some form of exactness in science. Yet in the realm of psychic difficulties and the impairment of the nervous system that lies so close to this that the two are inseparable, we have been most hampered by inexactness and difficulty of precise measurement and definition. It is needless to say that this does not pertain to the psychic side of the equation alone, for we are still too far away from any complete exactness of measurement on the purely physical side. How many centuries, for example, will have to elapse before scientific accuracy has become so refined or so well extended that all the physical factors which enter, both as cause and effect, into the disease picture at any one time in multiple sclerosis could really and all together be taken into account? While we are examining the renal output have we measured the registration of the disease process which pulmonary respiration might have given or the influence of the pulmonary intake or the facts which might have been discovered through sweat-glands or heart action or muscular postures or any other part of the vast field of bodily registration?

In the science of physics there are already certain well accepted mass units by which general physical facts may be determined and defined. In the activities of the living functioning human body we have only mastered a few. Experiment is multiplying these, but necessarily slowly, and meanwhile these processes, including those of disease, go on in large part unobserved and unmeasured. It is here that we cannot afford to neglect any new system of measurements which may have been discovered and been formulated in the psychologic realm. Not that these can claim a completeness which is present in the physical realm. That would not be possible in a realm, the psychic, which is limitless in comparison even with the multiplicity of the forms of body activities. Neither can it claim any hard and fast precision.

¹⁶ Jelliffe and Brink: *The Role of Animals in the Unconscious*, *Psychoanal. Rev.*, July, 1917, iv, 253.

Yet from the nature of psychic activity, be it in thought or feeling and their numerous intergradings, there is a unit of measurement which is ready at hand. Thought and feeling have always tended to express themselves in symbols. These I have called energy carriers.¹⁷ They may be conceived of as groupings of the sum of the affects and the mental processes stimulated by this affect, related to any object in the environment and the personal output of energy, corresponding to biologic needs, toward this object. The symbol becomes therefore the picture of the individual comprehension of any object or situation plus his energy activity toward it. Any symbol, therefore, chosen by the mental life, conscious or unconscious, stands as a chosen mass unit which measures the energy involved in any situation for which the symbol is used. May it not also be more than a mere measurement, for it may serve as well to define and locate this energy in the individual's grade of development or the level of his being at which this energy expenditure is made.

The psychotherapist is supposedly equipped with such a knowledge of the history of human development in terms of the individual's relation to his social environment that he can tell what are the forms of activity, of energy output demanded by the society in which the patient happens to live. He is able to define the higher intellectual form of the symbol by which the individual may seek free and effective expenditure of his energy to satisfy his personal requirements. This on the higher levels means the building up and healthy utilization rather than the tearing down of his machine, the body or some portion of it, in our case, as the spinal cord. If then the dreams reveal that in the unconscious, which is the larger portion of his mental life, he is utilizing not a symbol which is thus expanding opportunity and giving freer vent to energy, but one which refers to a long past no longer socially useful, may it not be seen that something is wrong?

At a remote archaic age when thought was simpler, feeling found its action pattern pathways more simply and more readily and the demands of a more complicated social standard did not exist. Now, however, thought, elaborating with the progress of culture, has built up a far more complicated form of demand. In order to keep pace with this, the body has had to learn through the widely extended psychic symbolism, to distribute its energy on many pathways, utilizing again the symbol for such energy expenditure. Now if it is seen through the dream that the symbolism, that is the picture of the individual's interest, confines itself to the simpler, more condensed archaic form may it not be conceived to indicate that the individual has abandoned (regression) or has never attained (fixa-

¹⁷ Jelliffe: *The Symbol as an Energy Container*, Jour. Nerv. and Ment. Dis., December, 1919, 1, 540; Tr. Am. Neurol. Assn., 1919.

tion) the higher levels. He has no lack of feeling, of affect, but its ways of discharge are confined. The energy that it represents cannot find healthy outlet. What more natural then than that there should have resulted from fixation or regression to such a level an infusion of energy into bodily pathways, a refilling of old channels which culture has relieved by the long building up of the wider mental activity?

These old action pattern pathways in the somatic territory have normally their sufficient task. In the well-developed individual the distribution of energy through widening of the symbol, the "soul" or "spiritual" development, has left the proper safe amount of functioning, of energy carriage, on any one of them. If, however, they receive such reanimation and reinfusion from the blocking of the higher pathways it can readily be seen that disaster may result. It is the confined power that destroys instead of running the engine.

Since, then, it is impossible yet to measure or accurately to locate the causes of the vascular exudative phenomena by employing purely physical concepts, it is at least justifiable to examine the psychic symbol with all they reveal of energy blocking, the attempts to use wornout ways of thinking and feeling, the reaching toward environment by clumsy primitive tools instead of through efficient modern methods. In the recognition of such symbols and in their use as measurements we ought to get some more definite and comprehensible idea of the struggle the energy is making and of the ravages it is causing, and why. Experience with the multiple sclerotic patient in psychoanalysis shows that this is a handle whereby the problem can be practically attacked with him and wherein also he in his reëducation can take hold to make a readjustment.¹⁸

2. Furthermore, in all of the patients there was extremely violent hate material held under the most forced repressions. None of the patients had freed themselves from the most infantile types of fixation on father or mother images. This might have been surmised from the characteristic "hysterical" personality of so many of these patients, using this word in the old sense.

3. For those who have taken the time or trouble to investigate the unconscious and are at all acquainted with the present-day conceptions I might add that very marked sister and brother fixations were present.

4. Sadistic anal erotic complexes were striking. These are intimately correlated with the unconscious hate situations.

5. The unconscious narcissistic homosexual components were found in all cases under extreme repression.

In all of the patients this last had produced the fear of the oppo-

¹⁸ Jelliffe: *The Vegetative Nervous System and Dementia Praecox*, New York Med. Jour., May 26, 1917.

site sex and had made marriage a nightmare or an impossibility—but none of the patients had had the courage to risk social censure and free themselves from what they projected as an intolerable burden. They thus repressed their hatred and made futile unsuccessful compensatory attempts.

I would like to present very briefly one small sample of the material which has given rise to the summary of findings just made. Thus one patient with a marked paraplegia, with foci in the lumbar cord, dreams the following archaic mythological fragment “*of a magnificent specimen, half horse above and half man below. He is struck with the magnificence and power of the lower extremities. This centaur-like being approaches a woman who fears him, but then acquiesces in his intentions, the horse part of the body having become less pronounced. It approaches her from the rear and would have intercourse, but by the vagina. There is no orgasm, but intense excitement.*”

These particular symbolizations which I have mentioned give examples of the intensified and compressed energy repressed to a very low level, which ought to be aroused to action to satisfy organic needs by bringing these into better relation with the environment. That at least is the only healthy action of energy. Here the energy is aroused but seeks to satisfy itself with goals which are no longer part of reality, or in relations which would be no longer of actual service to the individual in his adjustment to environment. They are the substitution therefore of fantasy rather than reality objects and situations. This does not give outlet and must drive the patient into the direction of a psychosis or, as in these cases, animate to excess body channels of an older level of activity. This makes it necessary for them to carry a task which is too heavy for them. Instead of the lighter weight of function, then, which ordinarily belongs to the spinal cord, it is asked to sustain an additional energy drive and breaks down. Enough of this energy, however, still remains in the psychic sphere to create the dream picture just given. The very nature of the picture and the features of the dream show that it cannot become the sufficient carrier of the energy, the pathway for its discharge. It is true that the dream is an aid in itself to the discharge of energy still lingering at lower levels but only to a limited extent. A more helpful dream is one that presents more of the progressive forward tendency and is accompanied in the waking life also by a greater ability to utilize adult, highly cultural levels of activity for energy discharge. Notice at the end of this dream the indication of its purely fantasy, non-effective character: “*There is no orgasm but intense excitement.*”

It can be conceived that there was a time in development when what we now call an archaic level, a more bestial¹⁶ or an animal level formed the highest cultural level of discharge. Let us say for argument that it was merely in that period of human history when man's own form was grosser, his attention to this physical life less

modified, less refined. Such an archaic repetition and choice of animal forms in the dream may represent this more animal nature of man or even a period when perhaps the life of animal and man was more closely associated than now; and when man, at least, like the child of today, felt less distinction in feeling and form and individual satisfaction from the animals about him than he does today. He attributed to the animal more identity of experience and feeling than would be possible for the adult today. The most humanized adult would have to confess today to some trace yet of this amalgamation even in his conscious thought. Clearer traces of the strength of such an amalgamation of conception, of the admission of animals freely to thought and feeling lie in those tales of ancient Greece and Rome which have been embodied so charmingly in Ovid's writings. He wrote in a later critical literary age, when such beliefs were relegated, among the most cultured at least, only to the poet's fancy. But he really spoke of and for an age that had hardly passed away. Early belief had represented a more serious mingling of human and animal experiences, at least in man's fantasy, human desire seeking itself in animal and through animal form. Poetry, especially such poetry of less trammelled Greece, could still take up such desire and open the gates for much of the energy expression which still lingered at such layers. Today, however, energy that tarries at such levels is blocked. Thanks to literary preservation we still have Ovid, and perhaps he should form more often part of the patient's curriculum for reading. He offers as it were a horizon toward which the mind looks out in its efforts to broaden its vision, more to broaden its scope of action.

The body's needs, our organic cravings, are very ancient. The mind is the sum, a constantly increasing one, of feelings and reckonings, thought permutations and communications concerning the needs and the feelings associated with them. *It is the organizer of all phyletic experiences.* This mind or psyche has always been at work casting and recasting symbols which represent shifting paleopsychologic horizons,¹⁹ widening vision, greater power and greater satisfaction through extension of horizons. The ability to look bravely out at each such paleopsychologic horizon and then mentally to cast and recast until that is in turn enlarged into another, represents progress and it represents health and lessening of inner tension through outer expression. Without this, thought and feeling become caught, fossilized in fixed layers, yet with this difference from geologic fossils—that in the mental world the fossils still live. The unreleased energy strains, struggles, and pulls whatever of individual striving and effort may have escaped back to its level or sorely divides the individual so that only partially effective

¹⁹ White, W. A.: *The Contribution of Modern Psychiatry to General Medicine*, Oster Memorial, New York 1919, p. 1228. Also *Foundations of Psychiatry*, loc. cit.

activity is possible on higher levels and a large part of the energy tears and destroys at the lower level. Either it is dragging at the personality and forcing it into separateness from the world in the fantasies of a psychosis or it is allowing its destructive activity on some somatic pathway as in these multiple sclerosis cases.

Energy means dynamic strength and this must exercise itself in one direction or another. Thus the necessity to open the horizon and then extend it again and yet again, which is the unending task of culture in the service of perfect health, or perfect health in the service of culture. For this there is no other tool than the symbol. This has been spoken of as an instrument for measurement, a mass unit. It is also a tool for forging ahead and maintaining the health of the whole personality, body and mind. By it the mind for itself and for the body gathers up the energy, lifts it out of its discarded level of an earlier passing or long passed culture, sketches the breadth and meaning of the new level and drives ahead into this.

Just how these compensatory efforts are prevented from getting out as compulsion neuroses²⁰ or a chronic neurosis of some type would make an interesting field for speculation; or looking at the situation from the point of view of making the body the scapegoat of the spirit, why do not these patients dissociate their conflict—develop a psychosis even if mild—and save the bodily structures. The catatonic makes an effort in this latter direction, but even then fails.²¹ Mysticism and religion are more successful.

Claude Bernard²² tells us that he hopes "some day the time will come when the physiologist, the philosopher and the poet will talk the same language and understand each other." I have often wondered if Hawthorne in the *Scarlet Letter* had not offered a striking illustration of the partial fulfilment of this wish of the great French physiologist when he wrote: "A bodily disease which we often think of as a thing apart and separate may, after all, be but a symptom of an illness in the spiritual part of our nature."

²⁰ Jelliffe and Zenia X.: Psychoanalysis and Compulsion Neurosis, *Psychoanal. Rev.*, April, 1920, vii, 134; Compulsion Neurosis and Primitive Culture, *Psychoanal. Rev.*, 1914, i, 361.

²¹ Kempf: Mechanistic Classification of Neuroses and Psychoses Produced by Distortion of Autonomic Affective Functions, *Jour. Nerv. and Ment. Dis.*, August, 1919, 1, 105.

²² See Preface to Kraus, Fr.: *Die allgemeine und spezielle Pathologie der Person*, *Klinische Syzygiologie*, Thieme, Leipzig, 1919.

THE SURGICAL TREATMENT OF EMPYEMA BY A CLOSED METHOD.¹

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THE surgical treatment of empyema has always been very unsatisfactory. The unusual prevalence of empyema during the World War made it one of the most discussed surgical subjects of this period and called forth numerous methods in attempts to lower the prevailing high mortality, which was 30.2 per cent. in the various army camps during the winter of 1917-1918. The so-called open operation which dates from the time of Hippocrates, with or without rib resection, was the method most generally used and will long continue to be used regardless of comparative results, because of familiarity and the inertia of custom.

For eighteen months the writer had charge of the empyema wards at Walter Reed General Hospital, Washington, D. C. and the Base Hospital, Camp Pike, Arkansas, and developed what may be termed a closed method. Immerman, in 1887,² described a method somewhat like the one about to be described, in that he inserted a single tube into the pleural cavity, air-tight and maintained negative pressure, but did not use a syringe to remove the fluid nor was any fluid injected. Since this time many methods, with some form of modification of the method described by Immerman, have been tried, with varied success.

This article is based on a series of 138 cases, 45 acute and 93 chronic, treated by the writer, with a mortality of less than 2 per cent., which is thought to be the lowest rate reported by any method in so large a series. Reports have been received from 80 per cent. of the cases, and no case, acute or chronic, is known to have recurred. It is believed the results attained by this method are sufficiently striking to warrant its being submitted as the simplest, the most efficient and the most practical of all methods for the treatment of acute empyema.

This method is clearly demonstrated in two reels of films, which are available gratis, for use by any medical school or medical society, by addressing the Curator of the Army Medical Museum, Washington, D. C.

¹ Read at the thirtieth annual meeting of the Western Surgical Association, Los Angeles, Calif., December 3, 1920. Read before the Illinois Section of the Clinical Congress of the American College of Surgeons at Peoria, December 17, 1920. Also read before the County Medical Society at Indianapolis, Denver, Salt Lake City, Ogden, Reno, San Francisco, Long Beach, Phoenix, Tucson, Kansas City, St. Louis and Louisville.

² See editorial note, Jour. Am. Med. Assn., February 1, 1919, p. 267.

Details of Closed Method in Acute Cases. Inasmuch as the success or failure depends upon many minute details, seemingly of minor importance, more space is given to the exact technic.

The place of election for operation is the eighth interspace in the postaxillary line. A diagnostic puncture at this point having revealed fluid containing microorganisms, the operation is performed at once regardless of the condition of the patient or stage of pneumonia. Care must be taken to prevent wounding the lung. To avoid this accident the needle puncture is made just before and always at point of puncture with a straight trocar, which should not have a long point. The cannula should be just large enough to admit snugly a standard Carrel tube.

The writer has found more than 2 c.c. of 0.5 per cent. procain unnecessary and has performed the operation 15 times without any anesthetic and with little pain to the patient. ^o

At the site of operation a stab not more than 5 mm. in length, through the skin only is made with a curved bistoury. The cannula is smeared with vaselin to prevent the edges of the tiny wound from clamping it. The patient should have the arm and shoulder raised, take a deep breath and hold it, thus separating the ribs as the trocar is inserted. The needle puncture, skin stab and insertion of the trocar can all be done in less than a minute.

The tube should be about fifteen inches long, seamless, and have from five to ten fenestræ, about 3 mm. in diameter and 1 cm. apart, within the cavity to facilitate the removal of fluid when fibrin clots are present. When the trocar is removed, instantly the tube is inserted through the cannula, which is now removed, leaving about six inches of the tube outside the chest.

The tube is held air-tight by the contracting wall of the wound and may be connected with a Potain aspirator, or the fluid may be removed by a half ounce bulb syringe,³ which is used in giving the treatments. Should the respiration become embarrassed from too rapid removal of the fluid it is advisable to stop a moment or inject 200 to 400 c.c. of Dakin's solution before continuing the removal. If the patient has a high temperature, with active pneumonia, normal saline is used instead of Dakin's solution, to cleanse the cavity. This is done by refilling the cavity nearly one-third and agitating the fluid in the cavity by quick compressions and expansions of the bulb.

The small dressing permits free chest expansion. A No. 00 safety pin is thrust through the edge of the tube. Two thin pads of gauze, each one inch square, split to the center, are placed over and under the pin. A pad two inches square of twelve layers of bandage gauze, with a hole in the center, made by a pointed and rounded instrument, and never cut, so as to admit the tube snugly, is then

³ The syringe and trocar used in this work are made by Becton, Dickinson & Co., Rutherford, N. J.

applied. Four strips of adhesive, each one and a half inches wide and three and three-eighths inches long, are applied so as to make the finished dressing square. This dressing will frequently last several days, as there is seldom any soiling around the tube unless the incision was made too large, or the patient have a very persistent cough, which should be controlled if possible. Should the dressing become soiled a razor blade is best to cut the dressing from the tube. Usually it will suffice to loosen one side of the dressing, change the two small pads and apply a new strip of adhesive. The patient can lie in any position without discomfort or danger of the clamps or tube becoming loose.

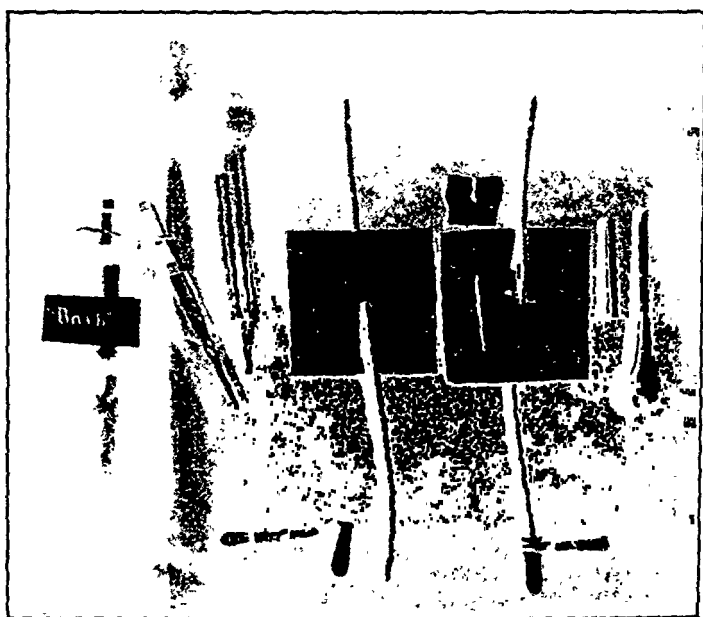


FIG. 1.—Shows individual tissue forceps, syringe and bottle for solution. The top and bottom of a typical dressing is shown, also trocar cannula.

Each patient should have his individual tissue forceps, syringe and Dakin's solution in a wide-mouth bottle where the syringe is kept between treatments. The forceps facilitates handling the tube in preventing air from entering during treatment and makes the wearing of gloves unnecessary. The end of the tube is kept sterile by being capped with the rubber from a medicine dropper held on by a Daefenbaugh clamp or spring clamp or clamp or bulldog clamp, which maintains the negative pressure.

In giving the treatment it is best that no air enter. The tube is first compressed with the tissue forceps, the clamp and cap removed, the nozzle of the syringe inserted with the bulb compressed and the secretions aspirated. From 50 to 200 c.c., depending on the size

of the cavity, of Dakin's solution are now injected and agitated. This is removed and the process repeated until the return is clear. An amount equal to about one-fifth the original capacity is now injected and left in from five to thirty minutes, then removed and the maximum negative pressure reestablished. The treatments usually are given every three to five hours by day and once or twice at night until the pyogenic membrane and fibrous exudate have been dissolved, a process taking from two to fourteen days, depending on the kind of infection, duration of case, size of cavity and the general condition of the patient. Subacute cases will tolerate more vigorous treatment, while cases with active pneumonia should be irrigated only every four to eight hours until the symptoms subside.

Glass piston syringes should not be used; unlike the bulb syringe, they are expensive, break easily, troublesome to sterilize and difficult to handle.

The suction power of the bulb syringe will lift water to a height of eight feet in a 6 mm. tube. That it will prevent pneumothorax is clearly shown by a radiogram taken just before and after negative pressure is established. Very little suction is required to expand the lung, and frequently the patient cannot endure the pain caused by the maximum negative pressure of the bulb.

When the tube is purposely opened, air immediately enters as the lung collapses to a certain degree, which depends largely on the adhesions and size of the cavity. If air so admitted is aspirated, the number of bulbs of air removed counted and the whole process repeated the number of bulbs of air removed will invariably be the same; furthermore, if after a maximum negative pressure is attained and any known number, say 5, 15, 30 bulbs of air are injected into the cavity and the process reversed, the number of bulbs of air aspirated will always correspond with the number injected. The same is true if a liquid is used instead of air, thus proving conclusively that the empyemic cavity can be entirely emptied of either air or fluid. The same is true regardless of the position of the patient or whether the tube is inserted at the most dependent part of the cavity.

That negative pressure is maintained for several hours is shown by the sound of air rushing into the cavity when the tube is left open, and the patient feeling a change of pressure or if the tube is connected to another tube leading into a bottle containing Dakin's solution the solution will be drawn into and fill the cavity.

When a large empyemic cavity is thoroughly cleansed and 150 c.c. of Dakin's solution injected and kept agitated a specimen withdrawn at the end of one minute will usually test about 0.38 per cent., and after five minutes will usually test about 70.0 per cent.

It is not essential that the sodium hypochlorite solution be 0.47 per cent., as 0.6 per cent. can be used for a reasonable time with

safety in the pleural cavity. With such a wide margin it is a simple matter for those who do not have the usual facilities for making and testing Dakin's solution to make up a solution sufficiently accurate from the various commercial products. Hychlorite is used now and found to be both convenient and effective.

After the amount of secretion and sediment have been greatly reduced, usually in four to ten days, and smears and cultures negative or nearly so, instead of continuing the treatment as before one should change to and inject a twenty-four-hour-old solution of 2 per cent. dilution of liquor formaldehyde in glycerin once daily for the following reasons:

1. Complete sterilization is attained in from three to seven days and the tube can be removed before the cavity is completely obliterated.

2. There is less discomfort to the patient and his sleep not disturbed.

3. The cavity is made to develop a tolerance for an antiseptic, which antiseptic is advisable to leave in the cavity, when the tube is removed, to prevent recurrence.

4. The resultant secretion following the injection of the formaldehyde solution forms unfavorable media for bacterial growth, and when sterile will be readily absorbed and the cavity obliterated.

The first two or three injections, which should not be over 5 c.c., will usually cause a rise of temperature, and for this reason should not be used too early in acute cases. The amount may be increased up to 15 c.c., but larger amounts are not necessary. Before each injection the cavity is given the usual treatment with Dakin's solution. If there is much sediment present the regular two-hour treatments with Dakin's solution should be given during the day and the formaldehyde solution treatment given once for the night.

It has been observed that both smears and cultures sometimes will remain positive for organisms for several days after beginning this treatment, even when the secretion gives a positive test for formaldehyde. There will be, however, a gradual decrease in the number of bacteria in both smears and cultures, and sometimes the latter becoming negative first.

Removal of the Tube. The original tube is not removed until the case is completed. Just before the tube is removed the cavity is given a thorough treatment with Dakin's solution and from 5 to 10 c.c. of formaldehyde solution is injected and left in the cavity. The dressing should first be removed and the skin cleansed with ether. An iodine swab is inserted in the sinus and rolled around the tube. The finger, one inch from the sinus, will compress the sides of the sinus during and after the tube is quickly removed, to prevent air from entering. The sinus is again treated with an iodine swab, the field cleansed with alcohol and the sinus closed with three wide strips of adhesive six inches long. Sometimes it is well first to make

two folds of skin over the sinus or apply a tiny alcohol pad. The second or third day it is well sometimes to remove the adhesive, treat the sinus and apply a similar dressing.

The amount of fluid secreted into the cavity after the tube is removed varies with the size of the cavity at this time, the number of treatments with the formaldehyde solution and the amount left in the cavity when the tube is removed. This, however, is a matter usually of small importance. If this fluid is sterile it will be absorbed sooner or later, or if necessary it can be aspirated, as in the ordinary sterile pleural effusion and the cavity gradually obliterated. If the fluid reaccumulates and contains organisms the general condition, failure to gain weight, physical signs and leukocytosis will be indication within a few days for the reinsertion of the tube, which was done in 5 cases, from whom the tubes were removed, very early as an experiment before sterilization.

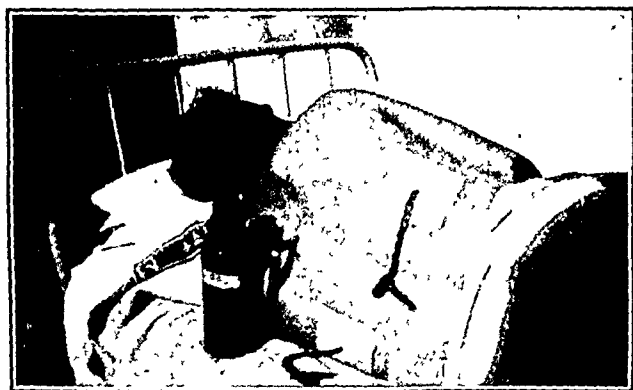


FIG. 2.—Bilateral empyema under treatment. Tube on right side removed in thirty days, tube on left side removed in twenty days. Operated when patient had bilateral pneumonia.

Importance of Diagnosis. The diagnosis of empyema is often difficult. There can be no doubt that many pneumonia cases die complicated with empyema undiagnosed. A large percentage of such cases diagnosed and properly treated could be saved. The diagnostic puncture or consultation in every serious pneumonia case would often prevent this grave error. The presence of the army doctor at the autopsy table during the World War did much to quicken his interest in empyema. It is believed that if a law were passed making it compulsory for every pneumonia death to be autopsied by a county health officer, or any other qualified person, in the presence of the attending physician and all other physicians interested, undiagnosed empyema cases would be less frequent and eventually fewer deaths.

Who, even of the laity, has not seen or heard of a pneumonia case after having passed the crisis, sooner or later, suffer a relapse or either die suddenly or linger along for weeks or months, and poss

years, then go to the grave with the death certificate signed "unresolved pneumonia" or "tuberculosis?"

Murphy was called in consultation once to see a patient which the attending physician said had had pneumonia for six months, but proved to be a chronic empyema.

Osler says: "In pneumonia the practitioner should be on the alert if the crisis is delayed or the temperature rises after the crisis, if chills and sweats follow, or if the cough changes to one of paroxysmal type of great intensity."

While the early diagnosis of fluid in the chest is important it is of even more importance to remove the fluid early and keep the cavity empty with the least disturbance to the patient. The effusion sometimes begins soon after the onset of the pneumonia and large quantities of fluid can collect within a few hours. Here we wish to state, with emphasis, that operation, at any stage of the disease regardless of pneumonia, by this method can always be done without the least danger of shock or collapse of the lung, and that those operated earliest after onset give the quickest and best results.

While the roentgenographic and bacteriologic laboratories are always to be preferred they are not absolutely essential with this method of treatment.

Exercise. No uncomplicated empyema case should be kept in bed. From the day of operation, graded, regular systematic breathing and calisthenic exercises are the quickest way to cause expansion of the lung and chest mobility. Unfortunately the novelty of the Woulfe bottles wears away too soon. Naunyn's plan was found efficacious: The patient sits in a chair compressing the well side against the arm of the chair, and taking long, deep breaths which force the expansion of the compressed lung. Only for the first few days after the tube has been removed should he refrain from exercise.

Food. The appetite is the natural guide for the kind of food. Abundant food is an all-important factor in treatment. The comfort of the patient and his ability to take exercise greatly aids the usually ravenous appetite. Many of the cases gained a pound a day for several consecutive days.

Empyema at Walter Reed Hospital. Twenty-three acute cases were operated upon at the Walter Reed Hospital. Eleven of these were reported by the writer² and 12 operated upon during the influenza epidemic. Of the latter group 9 cases were operated upon when the patient was either nearly moribund or had an active pneumonia.

Reports since September 1, 1919, from 7 of these cases show good condition. Four cases, 3 recently operated upon, had complications

and were still under treatment when the writer was transferred to another hospital. These 4 cases, before closed treatment method was completed, all had a secondary operation, with rib resection, followed by long, convalescent periods.

One of these 4 cases was very remarkable in that 7240 c.c. of thick pus were removed from the left pleural cavity at operation. A careful search of the literature reveals no record of a greater amount of pus ever having been removed at one time from one pleural cavity. The direct smear showed 60 bacteria per field and culture was pure *Streptococcus hemolyticus*. Negative pressure was impossible because of a bronchial fistula. Radiogram just before operation showed a dense shadow except the right upper chest and immediately after operation showed the left lung completely collapsed, which accounts largely for the complete absence of shock, although two hours were consumed in removing the pus. The fistula closed on the third day and the radiogram showed expansion of the lung, but the patient could not endure the pain caused by the maximum negative pressure. During the six weeks the patient was under closed method treatment; he gained twenty-five pounds, was still twenty pounds underweight and gradually improving. The patient was then subjected to rib resection and treated by the open method with Dakin's solution. Four months later he deserted, with his sinus still discharging.

One case of this group is the only acute empyema case the writer has had the misfortune to lose. This patient had been ill six weeks following influenza and pneumonia. He was nearly moribund, delirious, extremely emaciated; had positive blood culture, pericarditis, multiple abscesses and general arthritis, when a right trocar thoracotomy, in bed, yielded 1500 c.c. pus. The next day a left trocar thoracotomy yielded 2000 c.c. of pus. Radiogram now showed the chest clear and no pneumothorax. Before death, three weeks later, the blood culture was still positive.

Empyema at Camp Pike. The 92 cases treated at Base Hospital, Camp Pike, Arkansas, may be divided as follows:

Group I. Forty-nine acute cases operated by the Diederich method before January 9, 1919.

Group II. Twenty-two acute cases operated by the writer's method after January 9, 1919.

Group III. Twenty-one chronic cases admitted from other hospitals, having had open operations on an average of four and a half months previous.

GROUP I.

For some months Lieut. Diederich⁴ had been using a somewhat similar method, to be described later, but with many essential

⁴ Surg., Gynec. and Obst., April, 1919.

differences. Up to January 9, 1919, there had been 107 cases treated by the Diederich method at Camp Pike. At this time there were 74 cases remaining in the hospital, 25 convalescent and 49 still under treatment. Five of the 49 had been operated before October, 16 in October, 17 in November and 7 two weeks prior to January 9.

These latter 7 cases were closed on an average of twenty-six days after operation by more vigorous treatment with Dakin's solution and in addition the use of formaldehyde solution while the 25 convalescent cases had averaged fifty-one days with Dakin's solution alone. Most of the convalescent were in excellent condition. Two had a recurrence and were retubed for three and seven days respectively with no recurrence.

Of the 49 cases only a few had been operated before the pneumonia had fully subsided. An average of fifteen days had passed since the diagnoses of empyema and an average of five aspirations had been done before operation.

Thirty-six of the 49 cases were closed permanently on an average of eight days with the combined Dakin's and formaldehyde treatment. The cavities varied from 30 c.c. to 600 c.c. Roentgen-ray reports on many showed a pneumothorax. The remaining 13 cases had complications and required longer time. Three were bilateral empyemata, 9 had a bronchial fistula and 7 had necrosed ribs, due, it is thought, to injury to the periosteum at the time of operation and required resection.

Treatment of Chronic Cases Secondary to and Following Open Operations. While this treatment is not to be recommended the closed method may be instituted after open operation in acute cases which have been subjected to rib resection or intercostal thoracotomy and have failed of cure. Necessarily these chronic cases are usually more difficult to handle than acute cases originally treated by the closed method.

The sinus may be nearly closed and have to be dilated with a curved hemostat to facilitate the introduction of the small tube. Large sinuses require larger tubes so as to fit fairly snug and make possible negative pressure. In a few days the sinus will usually close sufficiently that the large tube may be replaced by a smaller tube.

The treatments are much the same but may be more vigorous than in acute cases. If the sinus is narrow and deep or the cavity so small that negative pressure is no factor, the tube should be inserted, almost full length of the sinus and at least twice daily the cavity filled to overflowing with Dakin's solution. Following each treatment in the smaller cavities enough formaldehyde solution should be injected to cause the resultant secretion to overflow around the tube. Sometimes it is best to give hourly treatments during the day and the formaldehyde solution but once during the night.

TABLE OF CASES, GROUP II.

No. of case. Name.	Onset of pneu- monia.	Aspiration.		Operation.		Side.	Character of fluid.	Organism.	Days tube was in cavity.	Disposition.
		Date.	Amount in c.c.	Date.	Amount in c.c.					
Case 1, W. McG.	Oct. 5	1.9.20	5	1.10.20	330	L.	Thick pus	Pneumo- coccus	16	Duty, Feb. 11.
Case 2, W. H.	Nov. 16	11.29.20 12.3.20 12.11.20 2.5.20	400 100 10 100	2.6.20	500	L.	Thick pus	H. S.	8	Duty, Mar. 27.
Case 3, R. B.	Oct. 26	3.7.20	10	3.8.20	325	L.	Thick pus	H. S.	7	Duty, Mar. 28.
Case 4, McK. R.	Dec. 23	1.17.20	800	2.1.20	1200	R.	Thick pus	Non- H. S.	36	Duty, Mar. 28.
Case 5, G. N.	Feb. 19	2.23.20 2.24.20 2.25.20	550 900 850	3.5.20	1800	R.	Serous	H. S.	14	Duty, Apr. 15.
Case 6, E. K.	Dec. 28	3.5.20	320	R.	Thick pus	H. S.	7	Duty, Mar. 31.
Case 7, L. O.	Jan. 17	1.20.20 1.21.20 1.22.20	1500 400 350	1.24.20	750	L.	Thin ser- ous	H. S.	42	Duty, Mar. 20.
Case 8, A. P.	Jan. 13	2.1.20	540	L.	Thin pus	H. S.	12	Duty, Mar. 24.
Case 9, L. H.	Jan. 9	1.16.20 1.23.20	1500 700	1.31.20	1050	L.	Thin pus	H. S.	21	Duty, Mar. 20.
Case 10, B. C.	Dec. 10	12.16.20 1.3.20	680 75	2.3.20	750	R.	Thick pus	H. S. Staphylo- coccus	12	Duty, Mar. 24.
Case 11, A. G.	Dec. 4	12.20.20	25	2.4.20	450	R.	Thick pus	H. S.	4	Duty, Mar. 27.
Case 12, H. W.	Jan. 4	1.8.20	30	1.14.20	2250	L.	Thin flaky	H. S.	29	Duty, Mar. 1.
Case 13, L. D.	Dec. 13	12.25.20 to 7 asp. Apr. 1. Dry	5400 5400	1.30.20 2.15.20	600 750	L. L.	Thin pus Thin pus	H. S. H. S.	9 19	Duty, Apr. 4.
Case 14, G. T.	Jan. 12	1.16.20 1.19.20	650 1040	1.30.20	2100	R.	Thick pus	H. S.	45	Duty, Apr. 7.
Case 15, H. W.	Dec. 18	1.3.20 2.2.20	100 50	2.3.20 2.21.20	300 100	R. R.	Pus; thin pus	Pneumo- coccus	10 23	Duty, Mar. 30.
Case 16, J. H.	6.4.20 6.8.20	800 300	R. R.	Pus Pus	H. S. H. S.	4 8	June 16, trans- ferred to Gen- eral Hospital, No. 12.
Case 17, A. S.	Apr. 2	4.15.20	10	4.16.20	1200	R.	Thick pus	H. S.	42	Duty, July 23.
Case 18, P. McL.	Feb. 24	3.2.20 3.3.20	550 1050	3.4.20	500	L.	Serous	H. S.	48	Duty, June 6.
Case 19, R. D.	Jan. 14	1.19.20 1.21.20 1.23.20 1.28.20	1475 1450 800 1800	1.31.20	1800	L.	Thin pus	H. S.	45	Duty, Apr. 15.
	mumps									

THREE BILATERAL CASES, GROUP II.

Case 20, R. H.	Oct. 3	10.24 to 1 4 asp.	11.7.20 2450	L.	Thin pus	Pneumo- coccus		
		2 asp.	400	R ¹	Heavy pus	Pneumo- coccus		
	...	11.28.20	1125	11.10.20	950	R.	Heavy pus	60	
	...			11.28.20	930	L.	Heavy pus	32	
		12.4.20	440	12.1.20	200	R ²	Heavy pus	49	
		12.4.20	440	12.1.20	200	L.	Heavy pus	49	
		11.30 to 1 10 asp.	1.1.20 2800	L.	Pus			
				1.31.20	300	L ¹	Pus	Pneumo- coccus	14	Duty, Mar. 3.
Case 21, H. T.	Oct. 1	10.9 to 10 4 asp.	14.20 1550	R.	Weight normal.
	...	10.21 to 1 15 asp.	9.20 3900	10.16.20	200	R.	Serous Serous	H. S.	40	Transferred to General Hos- pital No. 12,
Case 22, R.B.	Feb. 24	3.2.20 3.3.20	450 1050	2.1.20	700	L.	Pus	H. S.		June 16, bron- chial fistula.
	...	3.10.20	10	3.4.20	550	R.	Thin pus	H. S.	30	Small cavity.
				3.11.20	560	L.	Thin pus Serous	H. S.	20	Duty, May 20.

No case should be subjected to a Schede, Eastlander or Delorme operation under six months nor before strong negative pressure has been persistently applied for a reasonable time.

A secondary open operation is indicated under the following conditions; ribs necrosed from pressure or injury, a persistent bronchial fistula, multilocular or small irregular cavities and when the lung is held down by thickened pleuræ. After the secondary operation the wound should be closed, with a single tube leading air tight into the cavity, which is then treated as if originally a closed method case.

After a reasonable time though the cavity is not completely obliterated, if sterile, the proper amount of formaldehyde solution

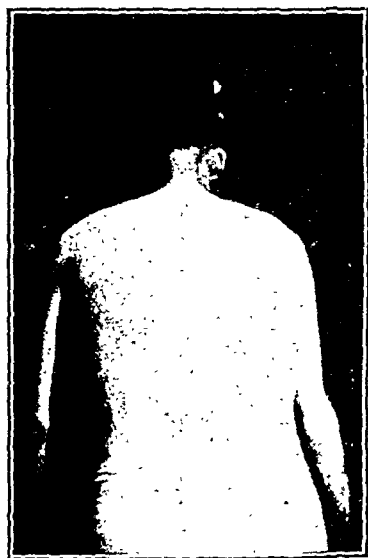


FIG. 3.—Bilateral case five weeks after operation. Returned to duty four weeks, later fully recovered. Shows size of scars.

should be injected and the tube removed. The unobliterated cavity will become filled with fluid, which sooner or later will usually be absorbed and the cavity gradually obliterated. At times it is advisable to aspirate two or three times generally following up with injection of small amount of formaldehyde solution, as was first used by Murphy.

Report of Chronic Cases. The following case is typical of the possibilities of this method. Pvt. J. M., August 31, in France, had sixth rib resected for empyema following pneumonia. Admitted November 17, 1918 to W. R. G. H. Condition fair, white blood cells, 12,000. Hemoglobin, 75 per cent. Poor right chest expansion. Copious purulent discharge from small sinus upper right anterior chest. Patient said there had been no change in his condition for

the last six weeks. A small tube was now inserted through the sinus and 660 c.c. thick residual pus removed. Smear showed 55 bacteria per field. Culture staphylococcus. Radiogram showed large pneumothorax. This cavity was treated with 200 c.c. Dakin's solution every hour by day and every two hours by night for forty-eight hours. The maximum negative pressure for the first day caused much pain, due to the lung expanding. During the next forty-eight hours only four treatments were given in which 300 c.c. of Dakin's solution were injected and left in for thirty minutes, then replaced by 15 c.c. of formaldehyde solution. Following the fourth treatment 10 c.c. of the latter were left in the cavity when the tube and original dressing were removed. The sinus was healed permanently two days later. The secretion aspirated twelve hours after second and third treatments was a clear, serosanguineous fluid and the smears



FIG. 4—Bilateral empyema six weeks after operation. Note full chest expansion.

and cultures of both were negative. December 16, patient had gained fifteen pounds; weight now normal; no pain; 150 c.c. yellowish serum were aspirated. Smear and culture both negative. Had no other aspirations or treatment. Chest expansion nearly full. February 2, returned from thirty days' furlough in excellent condition. Empyema cured.

The 21 cases of Group III, each had a discharging sinus and cavities from 20 c.c. to 750 c.c. The closed method of treatment was instituted and tubes removed in 12 cases on an average of twenty-eight days. No report from two but the other 10 cases show good condition with no recurrence to August 1, 1919.

Report of a Case of Group III. Name, H. R., November 1, 1917. Empyema. Rib resection. Healed September, 1918. Had been on a furlough two weeks when sinus opened. Two weeks later, February 1, 1919, was admitted to Base Hospital, Camp Pike, with

profuse discharge from a small sinus. A small tube was inserted through the old sinus and 750 c.c. of residual pus removed. Culture staphylococcus and streptococcus non-hemolyticus. March 3, tube was removed and sinus closed permanently in three days. March 24, returned to duty with full chest expansion and a gain of 26 pounds. September 2, reports excellent condition with no symptom of recurrence.

Transfer of Cases. On June 16, 1919, when the empyema ward at Camp Pike was closed, the remaining 21 empyema cases were transferred to General Hospital No. 12, Biltmore, N. C. Thirteen of these cases had been operated overseas by the open method. Three were admitted just before transfer and the others had been under closed method treatment too short a time to effect a cure. Of the 8 remaining cases 1 had been operated by the Phillips method, 4, Diederich's, and 3, the writer's method. Of the 4 cases belonging to Group I, all had complications and had been operated in October. Three cases, Nos. 16, 17 and 21 belonged to Group II. Case 16 had a bronchial fistula. Tube was removed June 10, and sinus healed permanently in a few days. Case 17 had gained ten pounds during the twelve days since operation. The tube was removed on the fourth day as an experiment, but had to be reinserted in two days. Case 21 was a bilateral case, with a persistent bronchial fistula, and required secondary operation.

The above 7 cases plus 2 more previously transferred and operated at Base Hospital, Fort Sam Houston, Texas, represent the residue of 129 acute empyema cases having had a trocar thoracotomy at Camp Pike. Most of the cases were of virulent *Streptococcus hemolyticus* infection and the mortality was only 9 cases, or 6.9 per cent. The mortality here had been 40 per cent. and at Walter Reed Hospital 32 per cent. with the open method as used at the War Demonstration Hospital, Rockefeller Institute, New York. Seven of the 9 fatal cases died during the influenza epidemic and all had complications, 4 of which were bilateral. Had these 9 cases been uncomplicated or even under normal circumstances, with plenty of help and room, they, too, in all probability would have lived. This is believed to be the lowest death-rate ever reported in so large a series of acute empyema.

Of these 9 transfer cases, only 6 of which having a secondary operation, after transfer to another hospital, compare most favorably to similar cases in other base hospitals of large camps, one of which, Camp Lee, Va.,⁵ when the empyema wards were closed in June, 1918, following the work of the Empyema Commission, had 140 cases transferred to General Hospital No. 12, Biltmore, N. C. These 140 cases had been treated by the open method with Dakin's solution, and more than half of them after transfer were subjected to major secondary operations.

SUMMARY OF THE 45 ACUTE CASES TREATED BY THE CLOSED METHOD.

Number of cases having a bronchial fistula	8
Number of cases requiring a secondary operation	1
Number of cases having a secondary operation before closed method treatment was completed	5
Number of bilateral cases	4
Shortest number of days tube was in cavity	4
Average number of days tube was in cavity ⁶	25.2
Number of cases which had tubes less than fourteen days	18
Number of recurrences	00
Largest amount of pus removed at operation	7240 c.c.
Average number of days patient was in bed after operation	7
Number of cases having but one dressing	8
Number of cases having not more than three dressings	20
Number of deaths (bilateral case)	1

Others Using the Closed Method. Capt. Manson, Chief of Surgical Service, Base Hospital, Camp Dodge, Iowa,⁷ reported 23 cases by the closed method, with a mortality of 8 per cent. In the conclusion of his article he states: "Our experience, we believe, justifies the opinion that the closed method thus described distinctly shortens the course of empyema, since it maintains constant negative pressure in the pleural cavity, prevents the collapse of the lung, promotes early adhesions between the lung and pleural cavity and prevents the secondary infections which are so common after thoracotomies. The simplicity of the technic, the minor character of the operation, the cleanliness and comfort of the patient and the economy of time and of dressing further recommend it as the ideal treatment of empyema so far devised."

Dr. Arthur W. Ralls reported in a paper before the Alabama State Medical Association Meeting, April, 1919, a series of 42 cases of acute empyema without a death by the closed method, during November and December, 1918, in the U. S. General Hospital No. 14, at Fort Oglethorpe, Ga.

He gives as factors favoring this method of treatment:

(a) This drainage is easily accomplished with the aid of local anesthesia only.

(b) Coughing is reduced to a minimum, whereas in costectomy the cough is painful and excessive for a few days.

(c) There is positively no shock, while the shock in rib resection is due to a collapsed lung and to disturbance of the natural pressure on the healthy side caused by the mobile mediastinum.

(d) There is not the added danger of secondary infection as in a large chest wound exposed often for dressings.

(e) The patient is more comfortable and cleanly and there is total absence of odor in the wards.

⁶ Average for 18 cases at Camp Pike was 20.2 days. This does not include the 4 cases which had severe complications and averaged fifty-six days.

⁷ AM. JOUR. MED. SC., August, 1919.

(f) It is possible to drain both cavities simultaneously if desired.

(g) By virtue of this method of drainage and the proper use of the blow-bottle and other lung exercise during convalescence, decontamination of the lung will be rarely or never necessary.

(h) Dakin's gives better results when confined in the cavity for ten to fifteen minutes. This cannot be done under the open method.

Dr. Charles S. White reported before the District of Columbia Medical Society, 12 cases with one death. The fatal case was that of a man, aged forty-five years, who had been delirious three days and moribund when 1500 c.c. of pus were removed at operation. This case followed a streptococcus laryngitis without pneumonia. Nine cases were operated in four different hospitals and 3 in the home. All but 1 case were cured in less than five weeks.

Dr. William C. Borden, Dean, George Washington University Medical School, reports 5 cases with no deaths. One was a bilateral case, both sides operated on at the same time, which he believes to be the first in the District of Columbia to recover, and he thinks the man undoubtedly would have died under any other treatment.

Dr. Anderson Watkins, Little Rock, Ark., reports 6 cases by this method, with complete recovery in from two to eight weeks, and considers the method superior to any method, new or old.

Not all have had as good results as these surgeons. Major Dodge, Camp Sherman, Ohio,⁸ reports 3 cases, all failures, by this method. He states they were operated on nine days after the onset of pneumonia; all were very sick and had large accumulations of seropurulent fluid which contained hemolytic streptococci. All seemingly went well and the tubes were removed the third week. Much disappointment soon followed when "roentgenograms showed that the collapsed lungs were not expanding to fill the space." It is evident that due care was not exercised to prevent collapse of the lung. Furthermore, had proper negative pressure been established and maintained in cases operated so early, adhesions would have formed, making impossible the "larger cavities," which Major Dodge states he later encountered. It is significant, however, that all three patients lived, even though secondary operations were performed, as compared to Major Dodge's mortality rate of 26 per cent. in 68 cases by the open method. He not only condemns the use of Dakin's solution in the pleural cavity, but would hasten back to the "pre-war methods," and as he so sarcastically says, "relegate to the boneyard all of the many fancy treatments of empyema evolved by the faddist who has been privileged to observe a series of cases for a limited period of time."

The main trouble usually is that the exact closed method technic is not followed carefully or some modification is used, and on failure the whole method is condemned. It is now and long has been the

⁸ Jour. Am. Med. Assn., June 21, 1919.

universal opinion that those loudest in their condemnations of the use of Dakin's solution are those most ignorant of its use.

Comparison with Other Methods. The method described by Phillips⁹ is much like that described by Immerman except that a metal cannula is left in the chest wall during the course of treatment.

In the Diederich method by means of a special trocar and cannula the rubber tube is introduced indirectly by passing beneath the skin and fascia then over the top of the rib before entering the pleural cavity. This he claims acts as a valve to prevent entrance of air but allow egress of fluid. We think no tube soft enough to collapse here should be used, for if the tube would collapse under such condition it would be an easy matter to force fluid by compression into the cavity but difficult or impossible to remove it, because under suction the compressed tube would further collapse and thus prevent the suction from reaching the pleural cavity. The treatments are less frequent, less intense and no formaldehyde solution used. The operations are delayed and repeated aspirations made until the patient has passed the crisis. Glass piston syringes are used.

The method of repeated needle aspirations with or without the injection of an antiseptic always means pain and a long convalescence with possible numerous complications. A case which can be cured by repeated aspirations alone in from four to ten weeks can usually be cured in as many days by the closed method.

The open method with its numerous modifications, whether costectomy or thoracotomy, is gradually becoming more in disuse for some form of occlusion treatment. The writer believes that the time will come when rib resection as a routine in acute empyema will be considered malpractice. Many advocate simply drainage, with or without irrigation. Others add sooner or later some form of negative pressure. The three-bottle gravity system which to a certain extent affords constant drainage is perhaps the most common of these methods. Caples, of New York, claims this method gives a pull of 20 mm. of mercury and that the normal negative pressure of the chest is 8 mm. The negative pressure of the bulb syringe is about 60 mm.

The large open wound not only necessitates large expensive dressings frequently changed but invites contamination and cellulitis, in addition to systemic infection from the wound itself. The shock following the collapse of the lung, further embarrassing respiration, not infrequently causes death within a few minutes or hours.

Most advocates of the open method are agreed on delayed operation preceded by repeated aspirations, as indicated, until the pneumonia subsides, and adhesions form to limit the collapse of the lung, making the operation more safe. This delay and repeated aspira-

⁹ Jour. Am. Med. Assn., May 3, 1919.

tions are not only unnecessary, by the closed method, but are decidedly harmful to the patient because of increased chances for complications. It is quite impossible to completely empty the chest by needle aspiration, as there is always danger of puncturing the lung with possible resultant bronchial fistula, pressure symptoms are only temporarily relieved, as a rule, the pleura gradually thickens, pus pockets form, the absorption of toxin continues and many complications might arise which are too frequently offered in the necropsy report as an alibi for this procedure, as the cause of death.

Major Stone, Chief of the Medical Service, Base Hospital, Fort Riley, Kansas, reported¹⁰ 310 cases of empyema, 37 of which were cured by aspiration alone and the remaining 273 cases were operated by the open method with a mortality of 48 cases, or 17.5 per cent. He also reported in the same article 100 deaths from empyema cases, which, as he states, "were not considered suitable risks for any kind of an operation except aspiration."

By virtue of a fair comparison with the writer's 2 per cent. mortality in a series of 45 acute empyemas of the above series would be 410 cases, with a mortality of 148 cases, or 36 per cent. This rate is perhaps a fair average with the open method when all cases are included, as they should be, and it is in keeping with the statement by Lillianthal¹¹ that a mortality lower than 25 per cent. in acute empyema may be considered good.

The writer has never seen an empyema case too serious to be operated by the closed method, and has operated early at least 25 cases, which either had an active pneumonia or some other serious complication with but a single death. In no case was there collapse of the lung or the slightest sign of shock, and all showed immediate improvement. There is every reason to believe that if all such extreme cases were operated by the trocar method most of them could be saved, even though a secondary operation, by rare chance, might be necessary.

Although the writer has had but 1 death, a bilateral case, in 45 acute cases, and 1 death, a bilateral case, in 93 chronic cases treated by the closed method, he believes that this extremely low mortality rate would obtain in even a much larger series of cases. Especially would this be true if the bad risks were not operated and only those cases operated as is usually done with the open method, who, by virtue of their own natural resistance or otherwise, have been enabled to survive the critical period and become good operative risks. Such practice, however, is believed to be not only a surgical sin but criminally wrong when early operation by the closed method offers quicker and better results, and a much lower mortality.

¹⁰ AM. JOUR. MED. SC., July, 1919.

¹¹ Military Surgery, June, 1919.

Conclusions. 1. Early operation by the closed treatment method has the following advantages:

(a) It can be done, regardless of the stage of pneumonia or serious condition of the patient, without the least shock or collapse of the lung.

(b) It provides complete evacuation of the empyema cavity, relieves cardiac and respiratory embarrassment and prevents the absorption of toxins and the usual resultant complications.

(c) It lessens the usual thickening of the pleuræ and prevents the lung, compressed by the exudate, from becoming fixed in compression.

2. The closed method has the following general advantages.

(a) Productive of great economy of time, labor and dressing material.

(b) Causes the minimum pain and discomfort to the patient.

(c) The dressing is small, lasts several days, without skin irritation and does not constrict the chest.

(d) Uncomplicated cases of empyema are not kept in bed.

(e) Cases are less likely to have recurrence, become chronic, or need a secondary operation.

(f) The constant negative pressure gives maximum expansion of the lung.

(g) The scar is very small and there is no chest deformity.

(h) Practical in the home and in country practice.

(i) The postoperative treatment in greater part may be done by a nurse or a properly instructed member of the family.

(k) Bacteriologic and roentgenographic laboratories, while always to be preferred, are not absolutely essential.

(l) The mortality is lower than by any other method.

(m) Can effect cure in acute bilateral empyema, both sides being operated at the same time, with acute bilateral pneumonia present, which treatment is impossible by the open method.

3. Dakin's solution, because of its great solvent and bactericidal action, is the most nearly ideal solution to use in the preliminary treatment of the empyemic cavity to dissolve the fibrinous exudate and partially sterilize the cavity.

4. Liquor formaldehyde in glycerin, 2 per cent. dilution, is the best solution to use in the empyemic cavity after the preliminary treatment with Dakin's solution, to complete sterilization, shorten the course of treatment and prevent a recurrence.

5. Smears and cultures after the formaldehyde solution treatment is begun will each show a rapid decrease in the number of bacteria, which are sometimes found two or three days in the smear after the culture will be sterile.

6. Bronchial fistulæ are more common than is generally suspected. With this complication salt solution should be used in amounts as large as possible and not cause the patient to cough.

7. A hypochlorite solution of increased strength over Dakin's solution in both alkalinity and available chlorin can be used in the empyema cavity with safety.

8. The available chlorin in Dakin's solution after injection into the empyemic cavity rapidly decreases. The strength after one minute averaged 0.38 per cent. and after five minutes 0.07 per cent.

9. Dakin's solution can be made with sufficient accuracy from various commercial products by those who do not have the usual facilities for making and testing this solution.

10. The progress of acute cases when less frequent treatments were given indicates that cures can be effected in a little longer time by giving only one to three treatments daily.

11. Cases becoming chronic following open operation generally can be cured in a comparatively short time by instituting the closed method treatment, so making unnecessary a major secondary operation of the Schede, Eastlander or Delorme type.

POST-NATAL DEVELOPMENT AND PATHOLOGICAL ORGAN RECONSTRUCTION IN RELATION TO FUNCTION AND DISEASE.

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Introductory Note. I present in the following pages a collective review of the results of investigations which have been carried on in my laboratories for a number of years, dealing with the constitution of important organs of the body at various age periods in health and in disease. Although incomplete, they have reached a point of practical interest, especially in the interpretation of pathologic function. It was therefore considered wise to collect at this time the evidence from various scientific journals and to place its general bearing and that of related subjects by other authors before a larger medical audience. Those interested will find the references to the documents in the case appended.

I. It is known that man during his post-natal existence passes through several more or less well-defined, great age periods, of which six are generally recognized:

1. **Infancy:** The period of extrauterine dependency upon the mother to the time of independent nutrition and motion (seven to ten months).

2. **Childhood:** The period extending to the time of second teething. Comprises beginning and development of independent motion, speech and senses (seven years).

3. **Presexual Age:** The period from end of childhood to beginning of puberty (the thirteenth to sixteenth year).

4. **Puberty:** The period extending to the end of length growth and sexual development (the twentieth to twenty-fifth year).

5. **Maturity:** The period of full individual development to the time of sexual cessation (about the forty-fifth year in the female and uncertain in the male).

6. **Senility:** The period of external decline to death.

In each of these periods the organization of the body possesses physical (anatomic) characteristics of its own. Certain structures atrophy, degenerate, waste by physiologic inflammation and are lost. New tissues appear or older structures acquire greater prominence, so that the relative importance of remaining organs is shifted.

The pathologic importance of these age periods has also been appreciated in a general way. Thus, infantile diarrheas and marasmus occur at the time of beginning independence from the mother when the gastro-intestinal tract and the organs of metabolism are forced to adapt themselves to the new environmental influences. Thus, also, infants, children and youths in whom the lymphoid tissue is highly developed display greater tendency toward infections which anchor with predilection in the lymphatic apparatus. Diseases of bones, either nutritive or infective, make their appearance mostly during the unstable period of active bone growth in which, moreover, the arrangement of the juvenile circulation exposes them particularly to entrance and arrest of infecting agents. It may be recalled in this connection that Lexer¹ and others obtained in young animals through simple staphylococcus injection into the blood an acute osteomyelitis which was associated with other manifestations of pyemia similar to those in children. The infective foci appeared, moreover, in those parts of bone formation which exhibit most active growth—that is the area between epiphysis and diaphysis which Kocher has named metaphysis. It was subsequently found that this area possesses in young bones a particularly well-developed system of end arteries which, taking their entrance from the periphery, advance by abundant arborescent division into the metaphysis. Embolic infection is therefore relatively easy in young, growing bones. In the adult, more stable, long bones this circulatory arrangement is reduced to lesser importance.

¹ Die Aetiologie u. d. Mikroorganism der Akuten Osteomyelitis, Sammlung Klin. Vorträge (Volkman), Neue Folge, 1897, eliii. Die Entstehung entzündlicher Knochenherde und ihre Beziehungen zu den Arterienverzweigungen, Arch. f. klin. Chir., 1903, p. 71. Kaufmann: Lehrbuch d. spec. path. Anat., 1911, ii, p. 685 (with extensive literature).

Corresponding to this anatomic change, Lexer observed that blood infection in older animals produced no osteomyelitis but a pyemia with joint and muscle manifestations and involvement of parenchymatous organs (liver and kidney). The conditions were therefore similar to blood infections in the human adult.

But not only early life stands under the influence of the age period: The whole time of puberty is largely under the ban of sexual development (chlorosis and mental diseases), and when in old age the tissues and organs experience the effects of wear and tear, the ground is prepared for the great group of involutionary diseases, arteriosclerosis, cancer and other senile atrophies and degenerations.

All these facts and similar evidence are well known, and I only mention them once more in passing. But it appears less appreciated that at least some of the important organs which persist through human life, and which we picture in our minds as more or less fixed in form and of a definite, permanent structure, in reality undergo important qualitative cell and structural modifications in different age periods, and that even within these periods organs are never absolutely fixed in structure and organization, but always fluid, constantly in regression and progression, ever changing.

Some years ago before I was fully aware of these facts and of their extent and importance, Dr. Lindsay Milne surprised me with some results of investigations he had carried on in my laboratory in New York on the histology of ductless glands, more especially the thyroid and suprarenal. He came to the conclusion that an absolute normal standard could not be found and that some changes which other investigators had put down as abnormal or as a disease might still come within physiologic limits. Similar conclusions were reached by Coplin in a study of the human thymus and by Theilhaber on the varying construction of the normal human endometrium.²

At about the same time I had occasion to examine the pancreas in several cases of severe diabetes mellitus in which the organ showed a marked not inflammatory, simple atrophy and collapse of architecture the cause and explanation of which remained obscure.³ It was not until Anderson and I⁴ stimulated by Reitmann's excellent study on regression and progression in the normal pancreas⁵ began to investigate the same problem that a probable explanation of this simple but essential atrophy occurred to us.

In conformity with Reitmann's results we found the normal

² Oertel: Degeneration, Senescence and New Growth, Jour. Med. Research, July, 1918, xxxviii, 3 (quotes the other literature in this connection).

³ Oertel: On Certain Changes in the Pancreas in Diabetes Mellitus, etc., Scientific Reports, Royal Victoria Hospital, 1916, Series B, i, 155.

⁴ Oertel and Anderson: Regressive and Progressive Changes in the Pancreas etc., *ibid.*, p. 163.

⁵ Beiträge zu Pathologie der menschlichen Bauchspeicheldrüse, Zeitschr. f. Heilkunde, Abth. f. path. Anat., 1905, xxvi, 1.

pancreas from infancy to old age a very unstable organ. Degeneration, atrophy, cell loss and acinar collapse are, to some extent, normal performances. But they are almost simultaneously compensated by formation of new cells, new acini and, in the growing, youthful pancreas even by formation of new lobules. Thus in the normal pancreas these processes are, as Reitmann first properly pointed out, balanced and coördinated, although, as Anderson and I had occasion to record, even there certain localized restricted abnormalities or faulty reconstructions may be noted.

The changes which I had previously discovered in the atrophic diabetic pancreas were similar to those Anderson and I saw in the normal organ. Only they had assumed much greater, diffuse and profound proportions and the regenerative attempts had remained incomplete, aborted and unbalanced. One could therefore in absence of any outside etiologic factor or inflammatory or nutritive interferences, interpret this pancreatic atrophy as an exaggerated, unbalanced physiologic performance, and it was possible to conceive a relation of such a condition to tumor growth.

An extensive investigation into the histology of the human spleen was subsequently carried out by Dr. Gross.⁶ Guided by our previous experience he set out to investigate three problems: (1) Is there a coherent cycle of changes in this organ in health during various age periods? (2) Is there any specificity in its reactions in disease? (3) Do the reactions of the spleen in disease differ with the age of the individual?

I refer to the original for detailed discussion and the tabulated and charted records of his result. It suffices here to emphasize that all these points were answered in the affirmative. So marked are the changes in all elements and organization of the spleen from infancy to old age that the two representatives at either end show little in common. To quote Gross's conclusions: "In early life the spleen, with its numerous endothelial buds, germinal foci in its Malpighian corpuscles, abundant capillary system and lymphoid elements, resembles granulation tissue. In its great vascularity it seems to have a structure admirably suited for thorough intermingling of blood and pulp. *Notable is that during this period the spleen does not react markedly to infection.* With progressive age the spleen becomes anatomically more unsuited to intimate contact with the blood. Bloodvessels thicken and become hyaline, the amount of lymphoid tissue, especially in size and number of Malpighian corpuscles, steadily falls, the splenic pulp gradually collapses and thus becomes relatively prominent. The trabeculae are also made more conspicuous, both by relative prominence as well as by actual increase in fibrous thickening.

"Thus it appears that functionally the spleen becomes more

⁶ Studies on the Gross and Minute Anatomy of the Spleen, Jour. Med. Research, January 3, 1919, vol. xxxix.

passive as age advances. But it is interesting that *the spleens of middle age show reactive exudative and proliferative phenomena in disease, in contradistinction to the behavior of young spleens.*

"In old age, finally, the spleen has undergone such marked regressive changes that its reactions and participations in disease are only very sluggish and uncertain." In other words, the adaptability of the spleen to environmental influences is, on account of its organization, greater when young. Its reactions, however, are greatest in middle age.

A number of observations which Dr. Waugh⁷ recently conducted on the bone-marrow gave similar instructive results and added to our previous knowledge of bone-marrow changes.

He found that the normal bone-marrow is to about thirty years of age parenchymatous and myeloplastic in structure, although it may grossly appear fatty. That is, it gives the appearance of an actively functioning organ of the hematopoietic system. As age advances the bone-marrow becomes increasingly fatty, never fibrous. Fat contents and parenchyma stand in inverse proportion. Young marrows show no fat. In later years (after thirty) this increases at the expense of the parenchyma, appearing first in islands between the parenchyma and thereafter shows many variations in its diffuseness and extent.

As far as erythroblasts are concerned these are numerous in young marrows, but this abundance drops off quickly as the second age period is reached. Apparently the erythrocytic function is not maintained in normal marrows to any great extent after puberty. But there is some evidence which, however, must still be confirmed by future research that this function in the adult rises and falls periodically in wave-like exacerbations of proliferative activity even in later age periods. Very interesting is that the erythroplastic function in disease does not seem to depend upon loss of blood cells alone but upon the character of the disease and the ability of the tissues to respond. Thus in infantile inanition, nephritis, endocarditis, goiter, or cancer low red blood cell counts in the marrow were recorded (as low as 3 per cent.). On the other hand in nearly every case of acute infection and in tuberculosis the count was 25 per cent. or over. In typhoid fever the values were low.

In other words regression is by itself insufficient to instigate or release growth, and either additional stimulating influences are necessary or proliferative attempts are extinguished by the same pernicious influence.

Lymphocytes occurred only in about the proportion in which they circulate in the blood. Plasma and endothelial cells (phagocytes) were seen only in abnormal conditions.

⁷ Studies on the Bone-marrow in Disease, McGill Medical Society, Senior Prize Essay, 1920.

The general conclusions which Waugh drew from his observations in different diseases, which I need not consider in detail here, were that the reactions of the bone-marrow are not uniform in various age periods, but necessarily vary with the temporary constitution of the marrow at the time of the disease and also with the irritating effect a particular disease may exert upon a bone-marrow of a certain constitution.

The organs which we have so far considered concern acinar and rather loosely combined cell structures in which stability may easily be upset through looseness in texture and which are open to easy environmental influences. But how does it stand with organs in which firmness and compactness combined with simpler uniformity of structure exists?

In other words are anatomic changes in age periods a general phenomenon in life of organs or are they confined to organs of loose and easily dislocated structure?

In order to contribute something to an answer to this question, Dr. Gross has carried on for several years a study of the circulatory tree of the heart in relation to its musculature and structure. He employed for this purpose a method consisting of a combination of an elaborated and perfected method of Spalteholz, with stereoscopic skiagraphs whereby very exact and detailed pictures may be obtained.

His results, which are now ready in monograph form,⁸ contain much useful information in regard to the structure and function of the heart in health and disease which I need not record here, but he has shown conclusively that in regard to its circulation and musculature the heart undergoes very profound changes from birth to senility. Briefly expressed these are—that the arrangement of the circulatory tree and, therefore, the blood supply which at birth are evenly distributed, are gradually shifted from the right to the left side, so that, as life advances, the left side becomes stronger in blood supply and musculature, the right side weaker. The senile heart possesses only a very small, insufficient right-sided supply. He has further pointed out how the auriculoventricular bundle (the so-called bundle of Kent or His) is originally provided for, how it is influenced by this altering blood supply and just how far and how extensive coronary anastomoses exist. So that, for example, the extent of interventricular septal anastomoses is an index of the age period.

Many pathologic functional disturbances are made clearer by this knowledge and by a comparison of pathologic hearts, prepared by this method, with others representing types of corresponding physiologic age periods.

With regard to kidney and liver I am so far only able to offer one

⁸ Gross: *The Blood Supply of the Heart* (in print). New York, Paul Hoeber.

or two more general, fragmentary statements. In the kidney we possess as yet no systematic detailed and classified knowledge, so that we are unable to state whether well-recognizable modifications for various age periods occur. There exists, however, evidence which points to the fact that its structure is not stable and permanent throughout. While glomeruli have already been found in embryos of 3 cm., they are said by some embryologists to be still forming after birth and to continue so far several weeks of infantile life. These new glomeruli are at first of very large size; after a year all glomeruli are of about equal size (140μ). Thereafter, from the second to the twenty-third year a uniform enlargement follows (to 240μ). In the newborn, glomeruli are only 118μ .⁹ We do not yet know whether there exists a general diminution in old age. Herxheimer¹⁰ has drawn attention to the frequent occurrence of hyaline glomeruli in the kidneys of infants and young children. He held them to be result of developmental anomalies, whereby the normal union between glomeruli and tubules has been interrupted. Since we are acquainted with the fact that in the fetus glomeruli and tubules form at first very rapidly, but, as Chievitz has shown, undergo in part regression and disappear, it seems more probable to regard these hyaline glomeruli as remnants of reduced renal substance. Similar hyaline glomeruli are seen in otherwise healthy adult kidneys without arterial disease.

Whether tubular reduction and reconstruction occurs to any extent in extrauterine life seems very doubtful. Actual new tubules are not seen to regenerate themselves after renal destruction, although the lining epithelium, especially of the convoluted tubules, possesses high regenerative activity in health and disease.¹¹

In the liver also we are as yet not sufficiently well informed to speak of or recognize a definite cycle of developmental events. But the frequent findings of localized cell regression and cell proliferation (as indicated by nuclear and cell division and differences in number, arrangement and proximity of cells in a unit) at least indicate here also a fluid condition. In an experimental investigation into pathologic changes in the liver of the rabbit in certain poisonings, carried on by me some years ago at Guy's Hospital,¹² I encountered many curious pictures in cell type and arrangement in liver lobules which were made clear after a study of a large number of normal and untreated rabbit livers from the collection of Dr.

⁹ Felix, W.: The Development of the Urogenital Organs in Manual of Embryology by F. Keibel and F. P. Mall, Philadelphia, 1912. Die Entwicklung des Harnapparats (1904); in Hertwig's Handbuch der vergleichenden und experimentellen Entwicklungslehre der Wirbelthiere, Jena, 1906.

¹⁰ Hyaline Degeneration der Glomeruli d. Niere, Ziegler's Beiträge, 1909, Bd. 45.

¹¹ Oertel: The Anatomic-histologic Processes of Bright's Disease, 1910, Philadelphia, p. 110, ff.

¹² Oertel: A Contribution to the Knowledge of Experimental Nephritis (Section on Pathologic Changes in the Liver of Untreated Rabbits), The Lancet, May 23, 1914.

Gordon Goodhart. It seems that these were physiologic performances. Recent observations of Weed¹³ on the cells of the arachnoid discloses also definite qualitative structural modifications in advanced age periods, notably in the appearance of newly-formed endothelial cell clusters.

With this evidence on hand there can be no doubt that the parenchyma of important organs is in constant flux, not settled and fixed. Moreover, and this seems to me a very important point, it has been demonstrated that at least in some of these a gradual but profound qualitative architectural reconstruction occurs with advancing age.

What then is the significance of these observations? These fall under a general and a special group.

A. General Conclusions. 1. Organs which normally exhibit a cycle of developmental changes in cell elements and tissue organization undergo corresponding functional modifications. Pathologic, anatomic and functional changes must therefore be interpreted in conformity and comparison with an age period.

2. The anatomic peculiarities and the fluid state of organs in various age periods have an influence on their dispositions to disease. Upon these factors depend, at least largely, immunity or susceptibility of age periods. Moreover, waves of regression and progression may here be of importance through upset of structural balance.

3. Anatomic and functional expressions of a disease vary in one and the same organ according to its construction and composition during an age period.

B. Special Conclusions. 1. Diseases may arise from the fluid and changing state and age progress of organs by loss of balance in physiologic regression and progression.

2. Depending upon the pathologic predominance of one or the other group of changes, essential atrophies; hypertrophies; degenerations; and progressive, destructive cell proliferation (tumor growth), all of which are normal developmental processes, may be duplicated and exaggerated in post-natal existence.

II. Cell and architectural reconstruction of organs which, as we have seen, plays an impressive role throughout physiologic evolution, assumes an equally great, though different, importance in those organs which are the seat of long-continued, slowly progressing diseases, more especially in the large group of chronic, productive inflammations. I propose, therefore, to deal in this second section with the relation of pathologic organ reconstruction to pathologic function.

The productive, clinically chronic, inflammations acquire here the greatest importance, not only on account of their frequency, but because they lead to the most profound alterations in essential cell

¹³ Johns Hopkins Bulletin, October, 1920, xxxi, 356.

elements and their arrangement. This has so far been definitely demonstrated in the kidney and in the liver, and it enables us to form a much clearer conception of functional derangements in these organs than we formerly possessed. Take, for example, the typical so-called primary or genuine contracted kidney. It is anatomically characterized by a progressive slow waste of parenchyma (glomeruli and tubules) and an abundant increase in fibrous connective tissue. That, briefly, is the essential tissue change, but we must, in order to appreciate its functional importance, construe the plan of the pathologic organ, for construction of an organ holds the key for understanding of its function not only in health but in disease. Here again the arrangement of the circulatory tree is basic.

The first one to draw attention to certain qualitative changes of the circulation in contracted kidney was Thoma.¹⁴ He demonstrated that with obliteration of glomeruli occurred a short circuit in cortical vessels so that afferent and efferent vessels connect without flow through a glomerulus. Subsequently, Ziegler and E. Kaufmann noted the unusual dilatation of pyramidal vessels and attributed this to the elimination of cortical circulation. These findings did not, however, make clear the greater and more profound circulatory alterations which were finally discovered after several years of experiments in attempts to inject and visualize the whole arterial tree by plastic, stereoscopic reconstruction. The technic of this process may be consulted elsewhere.¹⁵

It was found in the first place that the prevalent idea of normal kidney vasculature, as based on older methods of serial reconstruction is erroneous, and that instead of arcuate arteries which were considered to give off straight vessels to the cortex and medulla the normal renal circulation resolves itself into an abundant dichotomous division of arteries. The main renal artery divides rapidly into branches. These run until they reach the cortex, maintaining almost to the last a uniform diameter. Here they abruptly divide into numerous branches perpendicular to the capsule, and at right angle to these, glomerular branches are given off. The whole arrangement is that of a spreading chestnut tree.

What is the arrangement in the contracted kidney?

In the contracted kidney the normal cortical circulation is gradually eliminated, the remaining bloodvessels becoming narrow, tortuous and coursing without regard to the parenchyma. Its place is taken by a transfer and readjustment of the circulation to the pyramids which are not involved in the cicatricial contraction. Thus in a well-pronounced case the pyramids represent about four-fifths of total renal substance. The readjustment is carried

¹⁴ Zur Kenntniss der Zirkulationstörungen in der Niere, Virchows Arch., Bd. lxxi, p. 42.

¹⁵ Gross: Studies on the Circulation of the Kidney, First Communication, Jour. Med. Research, July, 1917, xxxvi, 3.

out not only by compensatory dilatation of vessels and pooling of the blood into the pyramids but by bloodvessels which in the normal kidney cannot be detected. An abundant compensatory circulation appears also in the pelvic fat and extends to and communicates with the pyramids! This new blood supply follows less faithfully the intricate course of the tubules, so that the inflammatory contracted kidney presents not only quantitative reduction but qualitative reconstruction of kidney vasculature. Herein lies a great point of distinction between it and the arteriosclerotic shrinkage in which these qualitative changes are not to be observed. Associated with this rearrangement in circulation is reformation in the remaining parenchyma. As far as this is not lost it undergoes alteration in secreting structures and course of tubules. The epithelium of the convoluted tubules regresses from a highly differentiated type to a low, syncytial, endothelial lining. Tubules are shortened, widened here, narrowed there, distorted in course, and not, as has already been said, accompanied by a normal, direct blood stream.

When we therefore consider these two essential groups of changes in contracted kidney (1) altered blood supply and distribution, and (2) loss and regression of secretory epithelium, with changes in the tubular course, we are in a better position to form a conception of this kidney function. For the new endothelial, membranous lining of the tubules can much less readily secrete the complex nitrogenous molecules which, moreover, it does not receive as directly as in the normal cortex. As much of these as is secreted will come from those parts of the renal substance which have as yet escaped the insults of the productive inflammation. It is therefore to be expected that the urine from these altered tubules is more of simple transudative character.¹⁶

In the medulla, on the other hand, instead of its normal simple and subordinated blood supply, appears an apparently new and enlarged network of blood channels which supplies the remaining loops of Henle and collecting tubules for compensatory and possibly new function.

Two of the most perplexing characters of contracted kidney—namely, the increasing abundant watery character of the urine and the increasing nitrogen retention which go hand in hand with parenchymatous waste—are brought nearer to our understanding. We have here the anatomic foundation for renal insufficiency and perversity.

In the liver also the tissue rearrangement in the productive inflammations commonly grouped as cirrhosis of the liver is profound

¹⁶ Gross: Studies on the Circulation of the Kidney, Second Communication, *Jour. Med. Research*, xxxviii, 3.

and functionally important. This had become evident to Kretz some years ago.¹⁷

Here it must be remembered that the degenerative atrophy of parenchyma and formation of inflammatory scar tissue follows in no way the normal architecture. The old classification into monolobular and multilobular cirrhosis can no longer be maintained, for the replacing growth of inflammatory granulation tissue never follows, from beginning to end, the configuration of the normal liver lobule. To the contrary its invasion and the separation of liver lobules is quite arbitrary, always intralobular, cutting off parts of old lobules here and there and uniting them to new liver islands. In these islands old cells unite with newly formed atypical liver cells to a new structural unit in new relations.¹⁸

The distinction, therefore, between inter- and intra-acinar cirrhosis falls down, but we may only differentiate between circumscribed and diffuse cirrhosis. A better name for the former is "insular type."

Concomitant with these changes in cell architecture go obliteration and rearrangement of old blood channels and bile ducts. Here the changes in vasculature resemble those in contracted kidney in loss of old and appearance of a new circulation. Milne showed that so-called, newly formed bile ducts are, at least largely, old ducts which in the new cirrhotic environment alter their shape and course and become more conspicuous. While much more could be said about these and other matters in cirrhosis, it suffices to show that in the liver also the architectural plan of remaining parts is so altered and partly new that it no longer has resemblance to the normal parent organ. Liver function is therefore not only quantitatively reduced by loss of parenchyma but qualitatively altered by the cirrhotic reconstruction. Metabolic perversities are to be understood and explained on this basis. Finally, the investigations of v. Hansemann and especially Reitmann (*l. c.*) of certain forms of fibrous pancreatitis also point to an entire reconstruction of the organ.

Enough has, I think, been said to make it clear that the human organism is never a stable and fixed entity in its parts and organs and that its functions are not uniform but differ qualitatively in various age periods.

What applies in this respect to the physiologic organism applies in even greater and exaggerated degree to the pathologic body.

But inasmuch as all organs in health and disease stand in certain relations to each other, forming the unit upon which the personal individuality depends, it follows that progressive changes occur in these relations in health and disease and that age and disease are

¹⁷ Kretz: Ueber Lebercirrhose, Wiener klin. Wchnschr., 1900, p. 2.

¹⁸ Oertel: On Lymphangitis and Perilymphangitis of the Liver, etc., Arch. Int. Med., 1908, i, 390.

anatomic expressions of reconstructed organs and of altered organ relations.

It has been said that the days of morphological investigation are over. I trust I have, although inadequately, indicated, that cultivation of morphology is as important for scientific vision today as it has been in the past and how much still remains here to be done.

THE TRANSFUSION OF BLOOD WITH REPORT OF 186 TRANSFUSIONS.

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THE brilliant results of human blood transfusion during the past few years and the ease with which this operation can be performed by any one of a number of modern methods has made it one of the most frequent procedures in practical medicine and surgery.

History. The early literature on the subject of transfusion is rather indefinite. In the year 1492 an attempt was made to prolong the life of Pope Innocent VIII by transfusion, which was unsuccessful. The lives of three donors were sacrificed in the attempt. A. H. Matthews, in the *Life and Times of Rodrigo Borgia*, flatly denies this occurrence. There are no convincing records of any transfusion being done before William Harvey's important discovery of the circulation. It was not until 1616 that Harvey presented his views to the College of Physicians, and it was 1628 when he published his treatise on *Motion of the Heart and Blood*.

Mention is made of transfusions by an Italian physician, Francesco Folli, in 1654, and by Daniel of Leipsig in 1664; but most historians give the credit to Wren of conceiving the idea of using infusions in bloodvessels and to Richard Lower, of England, and Jean Denys, of France, of being the first to really carry out the procedure. Lower carried out the first transfusion experimentally on dogs in 1665, and in 1666-7 Denys first successfully transfused a man by using lambs' blood. Lower used a cannula and connected the artery of one animal to the vein of another.

Samuel Pepys, on November 14, 1666, recorded in his diary that "at a meeting of Gresham College . . . the experiment of transfusing the blood of one dog into another was made before the society by Mr. King and Mr. Thomas Coxe upon a little mastiff

and a spaniel, with very good success." On November 21 he records that "the spaniel was produced and found very well." Again, on November 21, 1667, Pepys wrote of a "Poor and debauched man that the college had hired for twenty shillings to have some of the blood of a sheep let into his body . . . their purpose to let in about twelve ounces, which they compute is what will be let in in a minute's time by the watch." This was probably the first human transfusion done in England. It was accomplished by means of a cannula, at a meeting of the Royal Society at Gresham College, on November 23, 1667. The transfusion, according to Pepys was evidently successful.

There then followed many years of use and disuse, of success and failure. Animal to animal, animal to man and man to man methods were attempted. Some were done by means of a cannula, but the majority were done by the indirect method. That the failures were far greater than the successes can be seen in the action of the French Government, which forbade the procedure until the Faculté of Paris should give its approval.

Blundell, in 1817, reported seven cases of transfusion with human blood done for postpartum hemorrhage, three of which resulted in recovery. His apparatus consisted of a syringe connected by a two-way stopcock to a receptacle and to a tube, in turn connected with a cannula for insertion into the vein of the recipient. He had no means of preventing clotting. He reports that Goodridge used this method before him.

Sheele, in 1802, and Diefenbach, in 1828, wrote extensively on the subject of transfusion. Dumas and Prevost, in 1821, first showed the injurious effect of injecting the blood of an animal of one species into that of another. In 1835 Bischoff introduced the method of defibrination, and in 1848 Diefenbach also advised this method. Later Panum, Prevost and Brown-Séquard, after numerous experiments, decided that the process of defibrination was the chief factor in the performance of a successful transfusion. In 1863 Blasius reported 116 transfusions, all done in the previous forty years, 56 of which were successful. All of these were indirect transfusions. Two were from animals and were reported as successful. Fourteen cases were done with undefibrinated blood, all of which were unsuccessful. During the Franco-Prussian War, 37 transfusions were reported. All of these were done with defibrinated blood, and 13 were successful. Geselius and Hasse, in 1874-1875, respectively advised the use of animals' blood for transfusion, lambs' blood generally being used. No attention was paid to any reactions which would at this present day attract our immediate attention.

From 1863 to 1884 transfusion was supposed to be a "cure-all," and the claims made for it were preposterous. It was not until Landois, in 1875, demonstrated that the red cells of one species

when injected into a different species of animal are destroyed that all attempts at transfusing with heterogeneous blood cells were discarded. Panum, Landois and numerous other writers noted that blood of the same species might functionate normally if used for transfusion.

It was not long before the inadvisability of using defibrinated blood was discussed. Magendie, in 1838, noted several of the untoward effects after its use. Köhler, in 1877, made the important observation that the use of defibrinated blood or serum, even from animals of the same species, increased the danger, because of the excess of fibrin ferment injected, and therefore the increased tendency to intravascular clotting. Landois, Geselius and Ponfick agreed with this. Cohnheim, in 1883, in reviewing the literature, stated that it was inexcusable to use any blood for intravenous injection in which clotting had already taken place. But until von Bergemann, in 1884, published his important work, transfusion was still a subject of great interest. He reviewed the entire literature and came to the conclusion that the only reason there were not more fatalities was because in most cases not enough fibrin ferment had been introduced to produce extensive intravascular clotting. He came to the conclusion that the only permissible transfusion was the direct one from artery to vein. Such death-blows to a process already on the wane because of the frequency of its disastrous results, together with the fact that the use of saline solutions for intravenous injection was becoming more general, caused the transfusion of blood to be abandoned as a therapeutic measure.

From that time up to the beginning of the present century, transfusion is only rarely mentioned in the literature, and then chiefly as a matter of historic interest. In 1898, Crile, of Cleveland, began a series of experiments which marked the introduction of transfusion as a safe and valuable therapeutic procedure. He began by using arteriovenous suture, which came into existence through the work of Payr and Murphy. He later adopted the ring-cannula method, first suggested by Nitze in 1897 and carried out by Payr in 1900. Jensen, in 1903, experimented with several methods, and in his report favored suture technic. Höpfner, in von Bergemann's clinic, in 1903, used the ring method in twenty-eight cases and concluded that it was not applicable to vessels smaller than 3 mm. in diameter. The technic of vascular anastomosis became so perfected through the work of Carrel, of the Rockefeller Institute, that this method, in the hands of men experienced in bloodvessel surgery, came into vogue. In 1907, Watts reported four cases by this method. Crile's cannula method, as well as Carrel's method, presented so many technical difficulties for the average surgeon that other methods were sought for. Crile's cannula was modified by Janeway, Elsberg, Soresi, Bernheim and Levin. Elsberg's modification was undoubtedly the best.

Then in rapid succession followed the glass-cylinder method first advocated by Kimpton and Brown in 1913 and later by Vincent and Percy, with their modifications. After this, in 1913, came the syringe-cannula method of Lindeman. Ziemssen used this method twenty years before, but it never became popular until revived by Lindeman. After this, in 1916, came the simultaneous work of Lewisohn and Weil in this country, of D'Agote in Buenos Ayres and of Jeanbrau of Montpellier on the use of sodium citrate as an anticoagulant. Heretofore hirudin, ammonia and oxalates had been advised and used as anticoagulants, but each in turn had been discarded. The work of these four men reopened the entire subject of transfusion. At this same time (1916) Satterlee and Hooker described their pipette-cannula method.

Since then the modifications have been too numerous to mention. Brenziger, Martin and Lee, and Unger have described useful modifications. The chief fact to come out of all the recent work, however, is the fact that nearly all the blood from donors can be obtained by the needle, using one of the many described, and that in at least a large percentage of cases the blood can be given by the needle, thus avoiding the destruction of a useful vein.

Indications. Now that the initial enthusiasm for a newly rediscovered procedure is over we are better able clearly to define the indications for transfusion. As Bernheim has said, the indications depend upon the surgeon's knowledge as to "when the limit of bleeding has been reached; and by the limit I refer to progressive anemia of any sort, from any cause."

We have found the indications divisible into three groups, and increased experience in the procedure will give the clinician definite ideas of the types of cases which will benefit by it.

I. *Loss of Blood.* To this group belong all those cases of anemia from acute hemorrhage as well as those cases due to small, long-continued blood losses. Some of the latter, however, finally fall into the second group.

II. *Diseased Blood.* Transfusion for this group serves the following functions:

1. To stimulate hematopoietic function.
2. To increase coagulability.
3. To add to the oxygen-carrying capacity.
4. To increase the bactericidal or antitoxic properties of the blood.
5. To increase the general nutrition.

III. *Shock.*

I. **LOSS OF BLOOD.** 1. Blood transfusion is invaluable in acute hemorrhage after injury or operation. In this group belong the hemorrhages of childbirth, ectopic gestation, miscarriages, fibroids and other uterine hemorrhages. Acute bleeding from injuries, from gastric, duodenal or intestinal ulcers, and from rup-

tured viscera belongs here also. It is in these cases of acute massive hemorrhages that the surgeon sees the most miraculous results. One of our cases admitted cold, pulseless and unconscious after a crushing injury to the thigh was revived by transfusion of 2100 c.c. of citrated blood. These cases can be operated on much more safely and the convalescence is much more rapid with a transfusion than without. The average amount of blood which we use for transfusion in acute hemorrhage is 750 to 1000 c.c., although, as noted above, one of our cases had 2100 c.c. This, however, was distributed over a period of twelve hours. Free blood in the abdominal cavity, if uncontaminated, can be filtered and citrated and used to transfuse the patient.

The question as to when to transfuse for acute hemorrhage depends upon the surgeon, but we believe that if all borderline cases were transfused the mortality from acute hemorrhage would be less. A pale, cold, clammy patient, with a weak, rapid and thready pulse, dyspneic and often cyanotic, with a low red cell count and hemoglobin and a systolic pressure of eighty or below, should be transfused as soon as a suitable donor is found. This will not only make up for the blood loss but it will also undoubtedly help to check the hemorrhage, provided the amount of blood given is not too large or given in too short a time.

2. In the repeated small hemorrhages the anemia may become so aggravated that the blood picture will simulate that of a primary anemia. Transfusion before the hemorrhage is controlled, and after this until the blood picture again assumes a somewhat normal appearance, act nearly as specifically as in the first group. In cases of chronic bleeding the coagulation mechanism becomes deranged and the longer the bleeding continues the less likely it is to stop spontaneously, although the coagulation time of the blood outside of the body is but little delayed.

In these cases we transfuse repeatedly once or even twice a week, until the blood picture shows that the blood-forming organs are again functioning normally. In this way an apparently poor surgical risk may be turned into a good one.

II. DISEASES OF THE BLOOD. Here the new blood acts as a therapeutic agent.

(1) Hematopoietic Function. In this subsection belong the primary anemias and extreme secondary anemias. The transfusion is done with the hope that it will stimulate hematopoietic function. This probably occurs through the products of blood disintegration which stimulate the bone marrow. Several transfusions are necessary and it is often noted that the second transfusion is of much more benefit than the first. In this type of case we welcome a moderate reaction, since these patients seem to get the best ultimate results. For this reason some writers advise small doses of incompatible blood.

(a) *Primary Pernicious Anemia.* Vogel and McCurdy in 1913 first carefully studied the effect of blood transfusion and regeneration in primary pernicious anemia. In our series of cases we find that, while transfusion is of no permanent value, by repeated transfusions we have prolonged a patient's life for as long as four years. This patient has had sixteen transfusions, in this period, and is still able to go about. We feel that transfusion offers more for pernicious anemia than any other form of treatment. The remission which is brought about comes sooner and lasts longer, as a rule, than one occurring under medical treatment alone, and the life of the patient may be saved for some years.

If a remission is not brought about it is well to change donors. In this way results can be obtained by transfusion which make it superior to any other therapeutic measure. The important thing to remember is that under no circumstances should the patient be allowed to become so weak that transfusion is a dangerous procedure, but when the red cells continue to decrease and the hemoglobin reaches 30 it is time to begin transfusions.

(b) *Aplastic Anemia.* Here there is no tendency to blood regeneration, the leukoblastic and erythroblastic activity both being demoralized. Although blood transfusion does not even cause a remission in these cases, rapidly repeated transfusions (twice a week) will so increase the number of blood cells and hemoglobin, and relieve the symptoms that the patient can carry on his affairs for a variable period, though never a long one.

(c) *Splenic Anemia.* In this group we include splenic anemia and Banti's disease. Transfusion plus splenectomy offers the best opportunity for obtaining a cure. If the blood count is low after operation the transfusion may be repeated in order to give the blood-forming organs an impetus to resume their normal function.

(d) *Leukemia.* In our series we have had only one case of leukemia, that being a case of acute lymphatic leukemia. He was transfused four times, within ten days, with a total of 2200 c.c. of blood. When he was admitted his blood count was R. B. C., 905,000; W. B. C., 31,400; Hb., 25 per cent. On discharge his count was R. B. C., 3,600,000; W. B. C., 45,000; Hb., 33 per cent. However this improvement was only short-lived and an acute exodus followed soon after discharge. This is often the case and the most we can hope to do is to attempt to tide the patient over until the disease takes on a more chronic form and other treatment can be begun.

(e) *Hemolytic Ictero-anemia.* In this condition transfusion does not offer permanent relief but is of value in improving the anemia enough to warrant the operation of splenectomy, which is possibly a curative measure. Transfusion following the operation shortens convalescence and hastens the return of a normal blood picture.

(2) To Increase Coagulability. To this group belong the cases of (a) melena neonatorum, (b) hemophilia, (c) jaundice, (d) purpura, (e) secondary hemorrhagic diseases complicating such conditions as grave anemias, leukemias, and severe infections. It is in these hemorrhagic diatheses that we find the results of blood transfusion uniformly good. Melena neonatorum and hemophilia usually yield as if by magic to a single transfusion, although transfusion does not confer immunity to hemophiliacs against further hemorrhage. Citrated blood is just as efficacious in these cases as is unmixed blood. This has been definitely proved by Pemberton. If the first transfusion has not the desired effect, then a second one should be done with a different donor. Temporizing with less effective measures, as horse serum and various coagulants, may cost a life.

In our series we include a case of cholemia following cholecystectomy in which the patient had a number of fairly large hemorrhages. Her condition had become very serious when we decided on blood transfusion. There was immediate improvement in the patient's general condition and there were no further hemorrhages.

(3) To Increase the Oxygen-carrying Capacity of the Blood. Here belong the cases of illuminating gas-poisoning. Only a few cases have been reported. Carbon monoxide has a stronger affinity for hemoglobin than oxygen. When carbon monoxide combines with the hemoglobin the red corpuscle is removed from the circulation as effectively as in acute hemorrhage, as far as its oxygen-carrying capacity is concerned. The patient should be bled at the time of the transfusion. This may be difficult because the blood often becomes of a syrupy consistency. Our series of cases does not include any of this type.

(4) To Increase the Bactericidal and Antitoxic Properties of the Blood: Transfusion has no place in the acute infections unless the so-called "vaccination transfusions" suggested by Heyd and Hooker, that is, transfusion with immunized blood, open new possibilities. There is however, a large group of cases suffering from sub-acute and chronic infections which is materially benefited by transfusion. These cases, as a rule, are profoundly anemic, and transfusion should not be delayed until the body has lost its power of reaction. The transfusion is a stimulant to the hematopoietic organs, throws into the circulation functioning corpuscles and at the same time probably contains antibodies which may affect the life of the organism causing the infection, or so stimulate the patient's forces as to help them to develop an active immunity. Cases of chronic suppurating wounds do more than justify the procedure. We have used it in chronic suppurative disease of the hip-joint and in malignant endocarditis. The results would seem to justify further trial.

Antitoxic. For its antitoxic effect transfusion is of use in the toxemia of pregnancy with doubtful results, and in sprue, purpura and pellagra. While the beneficial effect is undoubted in purpura, in the other conditions the results are as yet doubtful. Lindeman reported four cases of tropical sprue treated by transfusion, with apparent recovery in every case. In the toxemia of pneumonia transfusion has been used with questionable results. Our only case, in extremity when transfused, died.

(5) As a Stimulant in the Various Cachexia. Here the transfusion is used for its general nutritive effect. It improves the vitality of the tissue cells. It frequently will permit radical operative procedure which before transfusion would have been out of the question. In debilitating conditions such as carcinoma it will improve the patient's general condition and prolong life. A field open to its use is the malnutritions of childhood, especially marasmus, and cachexia from prolonged diarrheas.

III. Shock. The value of transfusion in shock, especially if associated with hemorrhage, has received so much attention recently that it is needless to discuss it further here. It is just as useful in civilian as in military practice. In the cases of shock without hemorrhage, however, we must not expect as brilliant results as in those associated with hemorrhage. If an operation is necessary the patient who has been transfused is better able to stand the shock due to additional trauma.

DIAGNOSIS OF PATIENTS TRANSFUSED.

Pernicious anemia	32
Aplastic anemia	9
Hemolytic icterioanemia	2
(a) Both splenectomized.	
Splenic anemia	3
(a) Two splenectomized.	
Acute leukemia	1
Secondary anemia	4
Acute hemorrhage and shock	19
Acute infections	4
(a) Peritonitis.	
(b) Pneumonia.	
(c) Brain abscess.	
(d) Streptococemia.	
Cachexia and chronic infections	8
(a) Marasmus (2).	
(b) Nephritis, chronic (2).	
(c) Hip-joint disease (3).	
(d) Infectious endocarditis (1).	
Carcinoma and sarcoma	2
Hemophilia	3
(a) One case of cholemia.	
Total	87

Amount of Blood to be Transfused. The amount of blood to be transfused depends upon two factors: first, the indication, and

second upon the receiving capacity of the recipient. The latter depends upon the condition and size of the patient. In cases of severe acute hemorrhage transfusions of large amounts of blood are indicated. We have given as much as 2100 c.c. in a period of twelve hours. This amount is often difficult to obtain but 1000 c.c. can be taken from a donor in good physical condition without any risk. In cases of secondary, primary pernicious or aplastic anemia we usually use 500 c.c. although if the transfusions are not at very frequent intervals we use 750 c.c. In primary pernicious anemia if the blood count is fairly high and the transfusion is given to stimulate blood formation small transfusions, as 250 c.c., are as efficacious as larger ones. In hemophilia 250 to 500 c.c. are sufficient. In melena the size of the transfusion varies from 10 to 100 c.c. Whole blood is most frequently given intramuscularly in this condition.

The fate of the transfused blood has recently been determined by Ashby. He sums up his conclusions by saying "The life of the transfused corpuscle is long; it has been found to extend for thirty days or more. The beneficial results of transfusion are without doubt not due primarily to a stimulating effect on the bone-marrow, but, it is reasonable to assume, to the functioning of the transfused corpuscles."

Selection of Donors. In choosing donors for the transfusion three laboratory tests are necessary: the Wassermann reaction, a blood count, and typing. In an emergency the first two may be omitted, but under no circumstances the last. Even in children, when a parent is the donor it is a wise precaution to take, although Kimpton states that children under two probably belong to no group. Cherry and Langrock have proved in a series of 34 cases that all mothers can be used as donors in transfusions of their newborn infants; and Kimpton says in thirty transfusions with only two exceptions he has used the father. Pemberton, however, states that the infant develops its own group after the first few weeks. The donor should be a robust young adult, with a negative Wasserman reaction and negative venereal history, and a blood count that is high normal. He must be either in the same type group as the recipient or in group IV.

The interaction of the donor's and recipient's cells and serum may be determined by the crossed hemolysis tests, and these tests must be carried out in all cases where the type reading is doubtful. The simple typing with known sera has proved so satisfactory if accurately done that only in a few cases have we used any other methods for determining the suitability of a donor's blood. The method of Vincent, based on the grouping of Moss, is the one which has been used in most of our cases. A drop of known type II serum is placed on one end of a clean slide and a drop of known type III serum on the other end. One drop of the patient's blood is then mixed with each drop of serum. The slide is rocked from side to side gently

for five minutes and then examined for agglutination. The type is determined by the following table:

Serum	I	II	III	IV
Group I	—	—	—	—
Group II	+	—	+	—
Group III	+	+	—	—
Group IV	+	+	++	—

Moss has found in extensive observations that agglutination frequently occurs without hemolysis, but that hemolysis is always associated with or preceded by agglutination. If crossed hemolysis is done we use a modification of Rous' method of testing donor's blood for transfusion. Take two small test-tubes (1 x 5 cm.); in each place four drops of the following citrate solution:

Sodium citrate	1.5 gm.
Sodium chloride	0.9 gm.
Distilled water	100.0 c.c.

In one tube collect from the finger or ear one drop of the donor's blood and nine drops of the recipient's blood; in the other tube, one drop of the recipient's blood and nine drops of the donor's blood. Mix by shaking. Allow to stand for fifteen minutes. Take out a drop from each tube and place on a slide. Add a large drop of normal salt solution without mixing. Cover and examine under the microscope for agglutination. If desired, two drops of citrate solution and one drop of blood may be mixed in a third tube, as a control.

If there is no agglutination in any mixture, the transfusion is safe. If clumping is present in the tube containing nine drops of recipient's blood and one of the donor's, the recipient's blood agglutinates and may hemolyze the donor's blood and transfusion is dangerous. If clumping is present in the tube containing nine drops of donor's blood and one of recipient's it indicates that the donor's plasma agglutinates the recipient's cells. Transfusion under these circumstances is permissible since the donor's plasma is so diluted as to have little hemolytic power, but it is less desirable than where no agglutination is present.

Method. The method we describe here is the one in use at the University Hospital. After a donor has been selected he is placed on an ordinary operating-room table. The selection of the arm to be used depends upon the donor's choice and upon the suitability of the veins for use. The arm is extended and placed on a small table. The site is cleansed with a 95 per cent. solution of alcohol and then painted with a 5 per cent. solution of picric acid. A tourniquet is applied and sterile sheets are placed so as to surround the operative field.

A short length, large calibre aspirating needle is used to remove

the blood. We find this as efficient as any special needle designed for this purpose and the cost is considerably less. The needle is inserted into the vein against the current and the blood is collected in a suitable Erlenmeyer flask, which at the start contains one-half of the total amount of sterile sodium citrate solution to be used. We use enough of a 2.5 per cent. solution to make the end-result 0.25 per cent. While the blood flows into the flask the remainder of the citrate is dropped in with it by means of an ordinary pipette. The flask should be gently shaken during the collection of the blood (Fig. 1).

After the blood is collected the tourniquet is loosened and the needle removed. A small pressure bandage is applied. The flask containing the blood is inverted three or four times and then placed in a basin of water, the temperature of which is 120° F.



FIG. 1.

The recipient's arm is prepared in a similar manner, a tourniquet is applied, and if the vein is of sufficient size to allow it, a needle is used to introduce the blood (Fig. 2). If the vein is not large enough it is necessary to cut down on it and insert a glass cannula. This is, of course, less desirable where repeated transfusions are necessary because it destroys the vein for further use below this point. The skin is first infiltrated with a sterile solution of 0.5 per cent. novocain. The incision in the skin seldom needs to be longer than 1.5 cm. The vein is isolated by blunt dissection with a mosquito hemostat which is then inserted under the vein to carry the catgut ligature. The vein is tied off at its distal end while the ligature at the upper end is merely looped. Sharp-pointed scissors

are used to nick the vein in an oblique direction. A mosquito hemostat is applied to either side and to the apex of the triangular nick. While this is being done the assistant holds the proximal ligature taut so as to prevent unnecessary bleeding. The blood is introduced by gravity. A 250 c.c. cylinder containing a small amount of normal sodium chloride at 100° F., is used. The cannula is inserted into the vein in the direction of the flow as soon as all air has been excluded from the apparatus and the flow of saline is

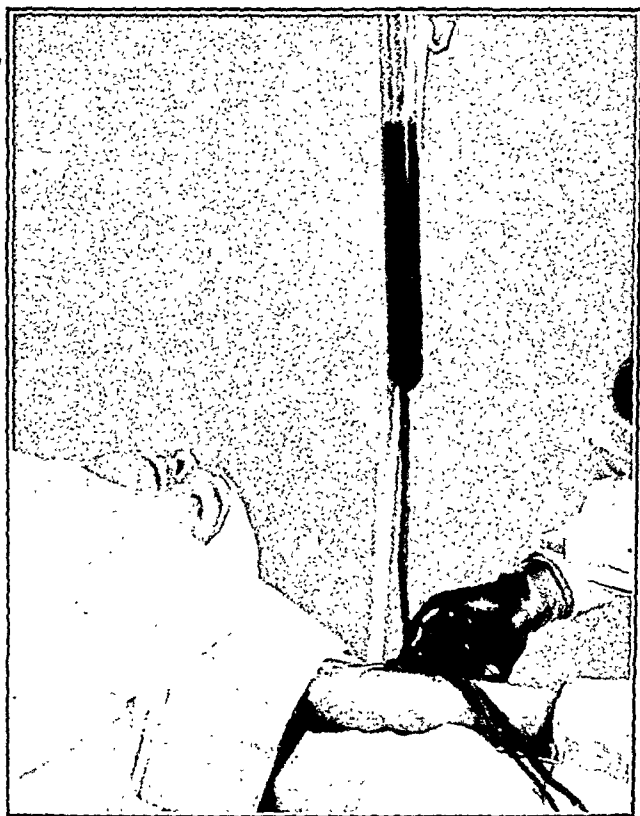


FIG. 2.

established. The tourniquet is now removed. The blood is poured into the cylinder, being filtered through several layers of gauze which have been placed over the top of the cylinder. Even though the blood has been typed and a crossed hemolysis has been done we stop the flow after the introduction of the first 25 c.c. to see if any immediate reaction occurs. If there is any reaction at this time the transfusion is stopped. The blood in the cylinder should be at a temperature of 110° F. and this may be accomplished by keeping the flask in a basin of water at 120° F.

After the blood has been introduced we again run in a small amount of sterile normal saline. The upper ligature on the vein is tied as the cannula is removed. The skin incision usually needs but one vertical mattress suture. In women accustomed to wearing short sleeves it is preferable to use the internal saphenous vein. This can be used for repeated transfusions, especially if the first incision is just above the internal malleolus.

When the vein is of sufficient size the same type of needle is used as that used in withdrawing the blood from the donor. It is inserted in the direction of the blood current. After the apparatus is prepared as above it is connected with the needle by a connecting piece.

In infants we have used the superior longitudinal sinus for the introduction of the blood. It is a very simple procedure and no untoward results have been observed.

Our series includes one arteriovenous suture, 47 transfusions by the Kimpton-Brown Method and 138 by the citrate method. We now use only the citrate method and consider this the procedure of choice. It is easy, safe, and as reliable as any method yet described.

REACTIONS.

None.	Mild.	Moderate.	Severe.	Death.
127 ¹	45	9	3	2 ²

In properly typed individuals there should be no mortality unless the transfusion is attempted as a heroic measure in a patient who otherwise has no chance at all.

In an emergency where time means all and the typing sera are not obtainable 15 to 25 c.c. of the donor's blood may be injected into the recipient's circulation. If no symptoms occur within three to five minutes, the transfusion may be continued.

The symptoms of incompatibility are: (1) Dyspnea, (2) pain in the back, (3) abdominal discomfort and even pain associated with nausea and vomiting, (4) dilatation of the pupils, (5) sweating and flushing of the skin, (6) vertigo and throbbing headache, (7) puffiness of the face and eyelids.

Ottenberg and Kaliski report that in 10 per cent. of their cases "febrile reactions or urticaria and other skin eruptions occur." These they say are irrespective of hemolysis or agglutination and are probably due to fibrin ferment or blood platelet destruction. Two of the patients in our series developed herpēs facialis the day following transfusion. A third patient repeatedly developed a

¹ A slight temperature with no subjective symptoms has been considered by us as no reaction.

² One by Kimpton-Brown method and one by citrate method. The deaths were both in cases of pernicious anemia. Since the writing of this paper one of the authors has had a mortality in another patient suffering from the same condition. The bloods were typed and cross-hemolyzed. The patient's condition, however, was most unsatisfactory. The temperature was 107° within six hours after transfusion and he died within twelve hours.

severe and annoying itching after each transfusion. Two developed bleeding from the gums with no other demonstrable symptoms except abdominal pain. Both of these recovered. In the serious cases jaundice and hematuria are evident if the patient lives long enough. Bernheim in 1915 in reporting 800 transfusions by 12 operators, found hemolysis in 15 cases with four deaths. Pemberton in reporting 1036 transfusions found 12 cases in which there were reactions, attributed to clerical errors in recording the grouping.

Meleny, Stearns, Fortune and Ferry in a study of 280 transfusions find that the more transfusions a patient is given the more likely he is to have a reaction, especially if the same donor is used a large number of times.

The temperature after the citrate transfusions has gone up as high as 104° F. It sometimes goes down in a few hours by a form of crisis, other times it takes two or three days to reach normal.

Mortality due to transfusion—1.09 per cent. It should be stated here that there have been more deaths in the series, but these occurred some time after the transfusion and therefore must be attributed to other causes.

Mortality figures are of little value unless it can be shown that death resulted from hemolysis or agglutination directly after transfusion because this is an emergency measure in many cases and death may result from the condition for which transfusion was done.

CONDITIONS OF PATIENTS WHEN LAST HEARD FROM.

	Unimproved.	Improved.	Cured.	Died.
Primary pernicious anemia	1	23	0	7
Aplastic anemia	4	3	0	2
Secondary anemia	0	5	0	1
Acute leukemia	0	0	0	1
Hemolytic-ictero anemia	0	0	1	1
Hemophilia including case of cholemia	0	2	1	0
Splenic anemia	0	0	2	0
Acute infections	0	0	1	3
Cachexia and chronic infections	0	6	0	2
Acute hemorrhage and shock	0	0	14	5
Carcinoma and sarcoma	0	1	0	1
	<hr/> 5	<hr/> 40	<hr/> 19	<hr/> 23
Total, 87.				

These records are not as accurate as they should be since there is no systematic follow-up procedure in the hospital. However some of the patients have been seen or heard from several years after their discharge from the hospital.

Conclusions. 1. With the element of risk practically eliminated blood transfusion has become one of the most effective procedures in modern therapeutics.

2. Transfusion is a specific in acute hemorrhage where the

"limit of bleeding" has not been reached, in melena and in the hemorrhage of hemophilia.

3. It is of definite value in primary pernicious anemia in hastening and prolonging remissions. It is indicated in cases of severe secondary anemia. After transfusion operations on debilitated or anemic individuals may often be safely undertaken that otherwise would involve serious risk.

4. Transfusion in shock is not as efficacious as in cases of shock associated with hemorrhage.

5. We have not been able to prove the value of transfusion in acute infections, but in chronic infections we have had results justifying its use.

6. Transfusion is of unproved value in acute leukemia. In aplastic anemia it is at the most a temporizing procedure.

7. The difference, as far as reactions are concerned, between the citrate method and the Kimpton-Brown method we have found to be practically nil and the simplicity of the former warrants its preference.

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A STUDY OF POLYCYTHEMIA VERA WITH SPLENOMEGALY, WITH A REPORT OF TWO CASES, AND A DISCUSSION OF THE TREATMENT BY THE ROENTGEN RAYS.*

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Definition. Polycythemia with splenomegaly is a disease in which there is an increase in the total number of red blood corpuscles and in the total volume of blood, usually associated with cyanosis and general weakness. This disease was first described by Vaquez in 1892, and Osler, in 1902, gave a more complete study of polycythemia, establishing it as a new clinical entity.

Etiology. The cause of the disease is unknown, but there are a number of theories as to its etiology.

Polycythemia vera occurs more frequently in men than in women, and usually occurs between the ages of thirty-five to fifty-five years. It is an insidious disease, lasting from eight months to ten years, the patient then dying from cerebral hemorrhage or from some intercurrent disease. Bence⁷ believes that polycythemia is due to a decreased capacity of the hemoglobin for oxygen. This being primary, an increase in the red cells takes place. This theory is supported by the compensatory polycythemia, which occurs in high altitudes where there is a lack of oxygen and the fact that inhalation of oxygen decreases the red cells. Lommel⁸ thinks the primary cause is stasis of the blood. Lefas, Rendu, Widai¹⁰ and others think the disease a primary splenic tuberculosis. Nechanin¹¹ believes heredity may play some part in the etiology of polycythemia. He tells of a case of a female student with a slight polycythemia, whose mother and sister each had cyanosis and an enlarged spleen. De Chapelle¹⁴ called attention to the history of injury as a cause of polycythemia. Three of Osler's cases laid great stress on some injury, a strain in 2 cases and the kick of a horse in the third. One case reported below had an injury to his neck in early childhood, and Stengel at that time thought that this might have played some part in the cause of the polycythemia.

The immediate causes of polycythemia have been variously ascribed to either a diminished destruction of the red cells, due to an increased resistance of the red cells to the hemolytic amboceptor, as was seen in one case reported by Pichard,¹³ or, on the other hand, an increased production of red cells.⁶

Symptoms. Cyanosis, general weakness, enlargement of the spleen, headache and constipation are the prominent symptoms of which the patient complains. In polycythemia the patients are particularly prone to hemorrhages.

* Read before the Pathological Society of Philadelphia, May 26, 1920.

Summary of the Blood Findings. The total amount of blood is increased. This is easily determined by the method of Haldane and Smith.²⁷

Red Blood Cells. The number is greatly increased, usually averaging about 8,000,000. In one case reported 14,180,000 red cells were found by J. Hnatek.²⁸

Normoblasts. Occasionally normoblasts are found. There may be some anisocytosis and poikilocytosis. The viscosity of the blood is increased in some cases to four or five times the normal.

Leukocytes. They run parallel, with the reds usually. There is a tendency to an increase in the percentage of the polymorphonuclear leukocytes.

Hemoglobin. This is markedly increased but not parallel to the increase of red cells.

Color Index. Less than 1.

Specific Gravity. 1050 to 1065.

The iron, lecithin and phosphoric acid contents of the blood are increased and the salts of the blood are normal.

Blood Serum. This has a low specific gravity, with a low protein content.

In some cases there is associated with the polycythemia a leukemic manifestation. In looking over the literature five cases have been reported in which myelocytes were found in the differential blood examination. Chief among these is the case reported by Blumenthal² in which he found the following blood picture: Red cells 11,450,000; white cells, 16,300; Hb., 110 per cent.

The differential count showed 45 per cent. myelocytes.

Pathological Anatomy. In reviewing the cases of polycythemia vera with splenomegaly and cyanosis there are only a few out of the total number reported that have autopsy findings of the bone-marrow included in the reports. Some of these autopsies were evidently carried out carelessly because the observations at the autopsy table were not supplemented by the laboratory examinations of the bone-marrow, spleen, etc.

The pathologic findings in the cases reported do not show any conformity in pathology, excepting the increase of blood in the bloodvessels of all organs. There is a hyperplasia of the erythroblastic and to a slight degree of the leukoblastic tissues of the bone-marrow. Red marrow is found in many places where yellow marrow is normally found. Westenhöpper¹⁵ compares the bone-marrow of polycythemia vera to that of a child. There are an excessive number of eosinophiles and bone-marrow mast cells.

Spleen. The spleen is decidedly increased in size and filled with blood. There is a mild hyperplasia of all the connective-tissue elements, and Hirschfeld¹³ found a slight myeloid transformation of the splenic pulp with an increase of the leukocytes and normoblasts. In some cases there are infarcts, in others tuberculosis of

the spleen and in one case of Senator's⁶ he found two areas of gummatous masses, although an antemortem blood examination showed the blood Wassermann negative.

Lymph Nodes. There is a lymphadenoid metaplasia, with an increase of the blood in these structures.

Autopsy reports collected from the literature:

Case of Wakasugi, K.¹ Bone-marrow. Medulla of sternum and ribs; dark red. Upper femur: Dark red; lower femur yellow.

Microscopic examination: All cells were found, *i. e.*, myelocytes, nucleated reds, eosinophilic and neutrophilic leukocytes and a few lymphocytes.

Spleen: Normal. No increased phagocytosis.

Conclusion: Hypertrophy of erythroblastic tissue of the bone-marrow.

Case of Rendu and Vidal¹⁰ de Moutard, Martin et Lefas:⁹ Conclusion: Fibrocascations; tuberculosis of the spleen.

Case of Cabot, R. C.:³ Red cells, 10,460,000; leukocytes, 20,000; hemoglobin, 120 per cent.; passive congestion of all organs; nothing clearly seen in the spleen.

Case of Saunby and Russell:³⁵ Red cells, 9,000,000; spleen enlarged, syphilis thought to be the cause; spleen of normal consistency; heart, hypertrophy of left ventricle.

Case of Türk:³⁶ Red cells, 7,500,000; hemoglobin, 112 per cent.; congestion of all organs; spleen congested; chronic tumefaction with anemic infarct; kidney, parenchymatous nephritis; apoplectic stroke the cause of death.

Case of Türk:³⁶ Red cells, 8,024,070; white cells, 26,300; occasional myelocytes; jaundice; enlarged liver, hepatic cirrhosis; enlarged spleen, chronic tumefaction of the spleen; bones, diaphyses uniformly red.

Case of Bauer:³⁷ Bone-marrow, no alterations; spleen, large; no other changes.

Case of Weber and Watson:¹⁹ Man, aged fifty-eight years: Red cells, 10,000,000 per c.mm.; white cells, 8000 per c.mm.; Specific gravity, 1.066; bone-marrow, hyperplasia of the bone-marrow; red bone-marrow was where yellow marrow is normally found; spleen, tumefaction of the pulp, all organs congested; heart, left ventricle slightly hypertrophied and aortic valves have an old vegetation; some plaques in abdominal aorta; stomach, ulcer on lesser curvature.

Case of Blumenthal:³ Red cells, 11,450,000; white cells, 16,300; hemoglobin, 110 per cent.; bone-marrow was hypertrophied. There were less fat cells than normal. The bone-marrow was embryonal in type because of the plethora; hypophysis, normal size; absence of chromophilic cells; spleen, enlarged, otherwise negative.

Differential count: Myelocytes, 45 per cent.; young myelocytes, 8 per cent.; specific gravity, 1065.

Treatment. There have been many treatments recommended for this form of polycythemia: venesection, splenectomy, drugs, roentgen therapy and radium. Except in a few isolated cases no permanent cure has been found. Clinicians have been puzzled as to the proper treatment because so little is known of its pathology.

It is the purpose of this paper to give our technic in the treatment of polycythemia by the roentgen rays, and, as far as possible, our reasons for the same. At the present time we can only suggest a method which is based upon the most likely pathologic features, basing it upon what we have thought to be the probable pathology.

There are two questions that confront us: (1) The origin of the disease, and (2) the cause of the splenic enlargement. If we can assume that the disease has its origin in the bone-marrow and the lesion is a primary hyperplasia of the erythroblastic tissues, then our treatment must be of the bone-marrow, with the view of inhibiting the formation of the red cells.

So little is known of the physiology of the spleen that it is difficult to say what is the cause of the splenomegaly. Various writers have attributed the splenomegaly to tuberculosis, syphilis or to a compensatory enlargement. There is some histologic evidence that the spleen destroys erythrocytes by the phagocytic action of the cells of the spleen, and it has been suggested that these cells liberate a ferment or hemolysin which acts extracellularly. Then if the splenomegaly is a compensatory process, attempting to provide for the increased destruction of red cells, our treatment should be with a view of stimulating these functions and not destructive as hitherto used.

The treatment of the bone-marrow in polycythemia vera was first suggested by Stengel in 1907, and at the present time we feel that primarily the bone-marrow should be treated, receiving an inhibitive dose and secondarily the spleen, it receiving a stimulative dose. After we had reached our conclusions on the treatment of polycythemia it was particularly gratifying to find that Krumbhaar,⁴² in 1918, suggested that such treatment was the most rational procedure for the treatment of polycythemia vera.

Technic. The details of the technic for the treatment of polycythemia vera is very similar to that outlined by Pancoast³⁹ for the treatment of leukemia. The only exception is in the treatment of the spleen:

1. The applications are made primarily over the bones of the entire skeleton, except the bones of the head, these being omitted, due to the likelihood of the loss of the hair in this region.

2. Each area is exposed regularly and systematically, and it is recommended that the maximum dose be distributed over three successive days rather than at one time.

3. Exactness in dosage is essential because we do not wish to destroy the bone-marrow, but to inhibit the formation of the red

cells, just as in hyperthyroidism we do not wish to destroy the secreting cells of the thyroid but to inhibit their hyperactivity.

4. Frequency: Daily exposures are advocated until the series is completed. Two areas may be exposed at one time, as in polycythemia we do not get the toxemia we get in leukemia.

5. Direct exposure of the entire spleen is given after the bones of the skeleton have been completed twice, and at this time we only give a stimulative dose.

6. Duration of the treatment depends upon the individual patient. However, three series are usually required before any stability in the blood counts are noticed. After the patient has received three series he should come in at intervals for inspection and blood counts should be taken, so that any premonitory signs, such as increasing red cell counts, can be discovered early.

Comment. This report is in itself preliminary. There are many points that need further investigation: for example, whether there is an increase in hemolysis or a decrease in the formation of the red cells, or both, during roentgen ray therapy of the bone-marrow; does the function of the spleen increase after stimulative doses of the roentgen ray; does the spleen enlarge after stimulative doses of the roentgen ray?

REPORT OF CASE.—This case has been previously mentioned by Pancoast:³³

W. J. B., male, white, aged forty-two years, weaver. Admitted to University Hospital May 3, 1905. Discharged June 16, 1905.

H. P. I. Patient admitted with history of repeated hemorrhages from bowel, nose and throat, and is in a general weakened condition.

H. P. I. Illness dated back seven years, at which time he began to have pain in the lower abdomen two hours after meals. The pains were paroxysmal and relieved by taking food. For the past two years he has been having hemorrhagic diarrhea, once having as many as twenty-one stools in twenty-four hours. The diarrhea lasts for a few days. One month before admission he had two hemorrhages, one from the nose and the other from the throat, both occurring while he was asleep. Bowels are constipated and the outer portions of the movements are streaked with blood.

S. H., F. H., P. M. H. Negative except injury to the sixth and seventh cervical vertebræ when he was six years of age, at which time the patient was hanged by a rope around his neck, causing a dislocation of the sixth cervical vertebra on the seventh.

Physical Examination. Patient is of raw bony development and poor musculature. His face and hands are cyanosed at times, especially after any excitement. The superficial lymphatic glands are slightly enlarged. Arteries are soft. Pulse not rapid and of fair volume and tension. Fingers stubbed. Head negative. Eyes: Conjunctival vessels injected. Scleræ are rather muddy. Ears and nose: Normal. Mouth: Tongue dark red, otherwise normal.

Neck: Has an angular kyphosis of the sixth and seventh cervical vertebrae. Thorax: small, soft parts poorly developed. Clavicles elevated, giving rather marked fossae above and below. Respiratory movements are costo-abdominal, the chest being held very rigid, only moving slightly up and down, with very little expansion. Heart outlines: Normal. Lungs: Apices retracted, bases extending to tenth dorsal spine. Diaphragm moves very little on deep inspiration. Percussion shows slight impairment over the right apex. Everywhere else normal. Breath sounds over the right apex show harsh inspiration and prolonged expiration. Elsewhere normal. No rales heard. Dulness begins at sixth rib. Abdomen: Liver palpable half inch below costal margin. Spleen palpable two inches below costal margin. Urine: negative.

SPLENIC AREA TREATED. (W. J. B.)

Year.	Date.	Blood, R. B. C	Year.	Date.	Blood, R. B. C.
1905	May 5	9,110,000	1908	Jan. 4	7,130,000
	W. b. c., 15,360; hb., 110 per cent.; smears of blood could not be made because of the increased viscosity of the blood.			11	7,510,000
	May 10	8,880,000		18	7,333,000
	W. b. c., 8800; hb., 100 per cent.			25	7,100,000
	May 18	7,940,000		Feb. 2	6,630,000
	W. b. c., 10,800			8	8,106,000
	May 29	8,260,000		15	6,130,000
	W. b. c., 11,200.			22	6,590,000
	June 15	8,450,000		Feb. 29	6,870,000
	W. b. c., 12,960.			Mar. 8	8,020,000
	Aug. 5	8,120,000		14	6,400,000
	W. b. c., 7,970.			21	7,870,000
	Aug. 14	9,000,000		28	6,556,000
	26	8,000,000		April 4	7,480,000
	Sept. 16	7,950,000		25	7,080,000
	30*	6,800,000		May 2	7,090,000
	Oct. 7	8,200,000		9	6,940,000
	21	8,250,000		30	7,390,000
	Nov. 18	7,600,000		June 13	6,550,000
	27	8,200,000		20	7,600,000
	Jan. 1	9,220,000		27	7,100,000
	13	8,800,000		July 11	6,870,000
	27	8,800,000		18	7,660,000
	Feb. 3	8,800,000		Aug. 1	6,740,000
	10	11,000,000		8	6,980,000
	24	9,240,000		12	6,600,000
	Mar. 3	8,800,000		Sept. 12	7,320,000
	10	8,500,000		26	7,400,000
	17	8,240,000		Oct. 3	7,020,000
	24	8,160,000		10	7,020,000
	April 7	9,030,000		17	6,300,000
	28	7,720,000		24	6,850,000
	May 12	7,110,000		31	6,350,000
	June 2	8,390,000		Nov. 7	7,630,000
	9	7,420,000		21	8,037,000
	23	9,430,000		Dec. 5	7,150,000
				12	6,150,000
				Dec. 19	7,360,000
				29	8,000,000

* The patient up to this time had received 240 milliampère minutes, distance 20 inches, 4-inch spark gap. No filter.

Year.	Date.	Blood, R. D. C.	Year.	Date.	Blood, R. B. C.
1906	W. b. c., 10,320; hb.,	135 per ct.	1909	Jan. 16	7,800,000
	June 30	9,080,000		23	8,070,000
	July 7	7,960,000		30	8,300,000
	14	9,150,000		Feb. 6	8,620,000
	Aug. 4	10,200,000		13	7,590,000
	11	8,840,000		20	8,060,000
	18	9,050,000		27	6,760,000
	26	8,530,000		Mar. 3	7,180,000
	Sept. 8	7,650,000		Apr. 10	6,920,000
	15	9,450,000		17	7,320,000
	22	7,710,000		May 1	5,900,000
1907	May 25	8,250,000		8	6,620,000
Treatment of the bone marrow				13	5,680,000
was started at this time.				22	6,600,000
	June 8	8,125,000		June 19	7,490,000
	15	7,450,000		26	6,720,000
	22	7,900,000		July 3	6,150,000
	29	7,780,000		10	7,080,000
	July 6	8,890,000		17	7,090,000
	20	9,260,000		24	7,460,000
	27	9,508,000		Aug. 14	7,780,000
	Aug. 3	7,230,000		Sept. 18	7,900,000
	17	6,520,000		25	8,040,000
	31	8,500,000		Oct. 2	8,300,000
	Oct. 5	8,200,000		9	7,640,000
	17	7,760,000		16	8,250,000
	Nov. 2	7,620,000		23	9,500,000
	9	7,920,000		Dec. 4	7,930,000
	Dec. 2	7,400,000	1910	Jan. 3	7,920,000
	9	7,730,000		Mar. 28	8,250,000
	30	7,210,000		W. b. c., 8700; hb.,	120 per cent.

Treatment of the splenic area was started soon after this patient came into the hospital. After what was considered a stimulative dose the red count fell from 9,110,000 to 6,800,000 (see Table). Treatment of the spleen was continued until 1907, the red count gradually increasing, reaching as high as 10,200,000 on August 4, 1906. Stengel suggested at this time the advisability of changing the method of treatment, *i. e.*, treating the bone-marrow instead of the spleen. This was done and a more encouraging result was obtained. The red cell count decreased to 5,680,000 and the patient felt much better physically for nearly a year. The blood count did not stay down, however, and the patient gradually returned to his original condition.

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**ATYPICAL TUBERCULOSIS WITH MIKULICZ'S SYNDROME:
REPORT OF A CASE, WITH UNUSUAL PULMONARY
AND SUBCUTANEOUS LESIONS.**

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I. Introduction. Tuberculosis of the salivary glands is sufficiently rare to excite interest. It is even more unusual to see it associated with tuberculosis of the lacrimal glands. The case which is here reported showed, besides these unusual localizations, a remarkable pulmonary affection and atypical tumors in the subcutis. The diagnosis, made on clinical evidence, was confirmed by histologic examination of excised tissue.

In 1888 and 1892, Mikulicz¹ called attention to a syndrome of chronic, painless, symmetric enlargement of the lacrimal and salivary glands, with freedom of the overlying skin from inflammatory reaction. Since then a large number of examples of the affection have been reported. In 1909, Campbell Howard² collected 67 acceptable cases from the literature and added 4 of his own. Each year three or four more are added, many conforming closely to the original description and many varying widely, including swellings of the lacrimal or salivary glands alone, and even unilateral swelling of a single gland. In spite of attempts to make of "Mikulicz's disease" a pathologic entity by excluding all cases due to ordinary tumor formation, tuberculosis, syphilis, sialodochitis fibrinosa and gout, it is usual at present to consider the affection as a syndrome, very much as are epilepsy and tetany. Accepting this conception, we have no hesitancy in classifying the case herein reported as an example of Mikulicz's syndrome.

II. Case. Mrs. S., a white American housewife, aged twenty-nine years, was admitted to the medical clinic of the University Hospital on June 16, 1920, complaining of tumors in the upper eyelids and about the mouth. Her family history, including that of tuberculosis, is of no interest. She married at twenty-one and her husband and two children are in good health. Her first pregnancy ended in a miscarriage at the fourth month; her other pregnancies terminated in normal deliveries. Her past history is of no interest, except for a submucous resection of the nasal septum in 1913, for itching of the external auditory canal; she was permanently relieved by the operation. Sore-throat and "head colds" have been rare.

¹ Berl. klin. Wehnschr., 1888; Beitr. z. Chir., Festschr., Theodor Billroth, 1892, p. 610.

² International Clinics, 19 S., i, 30.

She has had no symptoms at any time referable to the cardiovascular, gastro-intestinal, genito-urinary or neuromuscular systems.

Before the middle of January, 1920, she had been entirely well. At that time a small swelling appeared in the outer half of the upper eyelid on each side. It grew slowly for about a month until it reached the size of a large hazelnut, where it has remained stationary. There was moderate pain during its period of growth, but none since it reached its maximum size. In early March she noticed that it pained her somewhat to chew her food, and a swelling appeared behind the angles of her lower jaw. After a few days this reached its maximum size and the pain disappeared. Shortly



FIG. 1.—Photograph of case.

thereafter a similar swelling appeared on each side, just behind the symphysis of the jaw, and a few days later another pair in the lower side of her tongue, immediately behind the tip. About June 12 she noticed a small, painless tumor in the skin of the anterior surface of the left leg, just below the knee, and another a short distance below her left elbow. In the early part of April she developed a moderate unproductive cough. She states that there was a slight afternoon fever with this, never going above 99.6°. She had no night-sweats, no hemoptysis, no hoarseness and no pleurisy. She was told that she had pulmonary tuberculosis, and was sent to the Michigan Tuberculosis Sanitarium. From there she was sent to the University Hospital.

Examination showed a poorly nourished woman in early adult life. In the outer half of each upper eyelid was an irregular, nodular tumor about the size of a large hazelnut. It was almost cartilaginous in its hardness and was completely without tenderness. There was a partial ptosis of the lids, so that the palpebral fissure was triangular, with the base toward the nose and the pupil partly covered, giving her an appearance that has been aptly compared to



FIG. 2.—Roentgen ray of chest.

that of a blood-hound. The conjunctivæ were normal and there was no gross disturbance of vision. There was a general symmetrical enlargement of the salivary glands. The parotids were as large as small eggs and the submaxillary and sublingual glands were as large as hickory nuts. In the lower lip, near its outer ends, were a pair of glands as large as peas, and there were another pair under the tip of the tongue about the same size. All were extremely hard, and

were entirely non-tender. The mouths of the gland ducts were normal. The thyroid isthmus was firm and easily palpable, about the size of a lead-pencil. The percussion note was impaired over the upper part of both lungs, tactile fremitus and whispered and spoken voice were increased, and there were a few persistent, fine crackling rales; the breath sounds were here of the bronchovesicular type. The spleen could not be felt and there was no general lymph adenopathy. In the subcutaneous tissues of the anterior surface of the left leg just below the knee was a small soft, easily movable, non-tender tumor the size of a pea. A similar tumor was



FIG. 3.—Photomicrograph of a piece of salivary gland from lower lip.

found over the left ulna, just below the elbow. As was true of the glands, the skin over these tumors was not apparently involved in the process.

She was referred to the otological and ophthalmological clinics, both of whom stated that their special examinations revealed no pathology except that described above. Two roentgen-ray exposures were made of the chest. The plates were not characteristic of pulmonary tuberculosis, and from them the diagnosis could not be carried further than that there was "some sort of interstitial sclerosis." The roentgenologist believed that the picture could easily have been caused by the tubercle bacillus. Tangential expos-

ures of the face failed to show any shadows suggesting calcification in the enlarged glands.

The urine was at all times normal and the blood-pressure was 120 systolic and 70 diastolic. No sputum was obtained, even after the administration of potassium iodide. Wassermann's reaction on the blood was negative. Repeated examinations showed the blood entirely normal. The hemoglobin was always between 85 per cent. and 95 per cent. on the Talquist scale, the red cells were between 4,600,000 and 4,830,000 and the leukocytes between 4600 and 7650. Stained smears of the blood showed no abnormalities

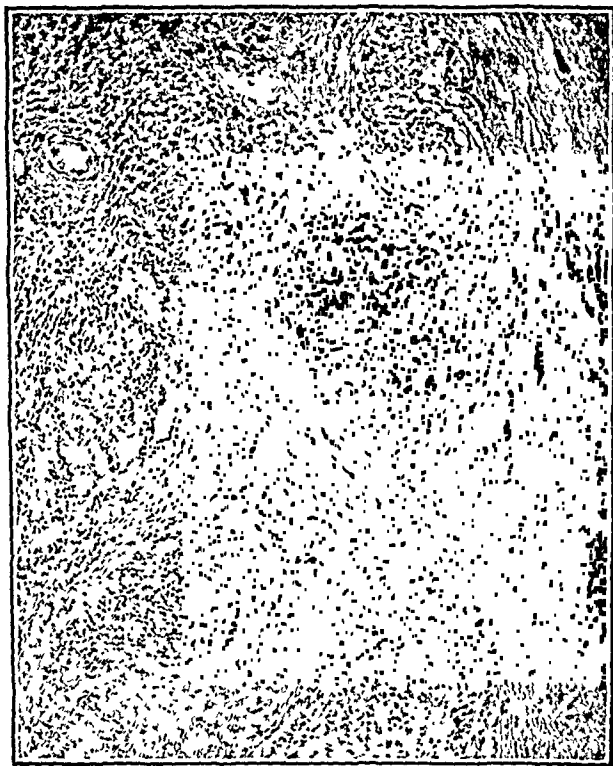


FIG. 4.—Photomicrograph of piece of subcutaneous tumor.

and the differential counts were all normal. One-tenth of a milligram of Koch's old tuberculin, injected subcutaneously into the arm, produced a definite febrile reaction, though she had had no fever before. A half a milligram, injected after the patient had been afebrile for a week, produced a typical fever, with subjective symptoms of malaise.

During her stay in the hospital her temperature and her pulse and respiratory rates remained normal. The enlarged glands showed a striking tendency to resolve, and by July 15 the submaxillary and sublingual glands were not palpable and the parotids had decreased noticeably in size. The subcutaneous tumors increased

in number, though not in size, until on July 15 it was noted that there were a dozen or more on each arm and leg. There was no apparent grouping of them, and all were about the size of peas. They were in the subcutaneous tissues, freely movable and free from tenderness. The skin over them was not changed. The tumors resembled more than anything else the tumors of multiple fibromata of the skin. When the patient left the hospital on July 20 she agreed with us that there had been further diminution in the size of the parotid swelling, though her only treatment had been rest, a high caloric diet and, empirically, syrup of iron iodide. The lacrimal glands appeared no different from their condition at entrance.

One of the enlarged accessory salivary glands was removed from her lip, and a subcutaneous tumor from her lower arm and examined microscopically by Dr. A. S. Warthin. The report from the department of pathology is as follows:

Salivary Gland. "Description: The specimen consists of a mucous salivary gland and a small lymphoid node. Throughout the gland there are numerous miliary tubercles, consisting of sharply circumscribed avascular epithelioid nodules, containing many characteristic giant cells. These miliary tubercles occupy the rudimentary lymphoid nodes of the gland. In a number of areas around the larger ducts they are conglomerated into larger masses of epithelioid tubercles. These tubercles show almost no tendency to caseate. The epithelioid areas themselves are completely devoid of blood-vessels, although in the agglomerated nodules, remains of capillaries can be found at the borders, and between the miliary tubercles there is a slight lymphocyte and plasma cell reaction about the tubercles. The picture is that of an avirulent non-caseating tuberculosis seen in some cases presenting the clinical picture of Hodgkin's disease, in which there is a systemic involvement of all the lymph nodes. As a rule it is very difficult to demonstrate tubercle bacilli in these by staining. From the appearance here I believe that this is an avirulent form of tuberculosis, probably bovine and similar to that found in some cases of generalized tuberculosis of the lymph nodes, as mentioned above."

Subcutaneous Tumor. "Subcutaneous tissue. This is apparently a hyperplastic rudimentary lymph node surrounded by striped muscle. It is very edematous, probably from an injection of a local anesthetic. It consists of centers of avascular epithelioid miliary tubercles, encapsulated by fibroblastic and mature connective tissue. About this there is a very marked inflammatory reaction with new bloodvessel formation and polynuclear and mononuclear infiltrations, a secondary infection or inflammatory reaction, due to some other cause. The appearance of the miliary tubercles here is spoiled more or less by poor preparation and the edema, but the same non-caseating avascular epithelioid nodules are shown, but with few giant cells."

III. Diagnosis. The clinical evidence, combined with the histologic examination of the extirpated tumors, puts the diagnosis of tuberculosis beyond doubt. Had any one of the lesions—the pulmonary fibrosis, the tumor of any one gland or pair of glands, or especially the subcutaneous granulomata—been presented alone there would have been more than a little difficulty in running down the etiology. The occurrence of all this remarkable pathology in one patient is of great interest as a suggestion of the bizarre ways in which the tubercle bacillus may make known its presence.

May we reasonably add this to the group of cases which have been collected under the name of Mikulicz's syndrome? This opens the argument as to whether or not the name of the German surgeon should be applied only to those cases in which the glandular swellings are lymphomatous, or to all cases of chronic painless, symmetric swelling of the lacrimal and salivary glands.

Clinically, without biopsy, the tumors about the face were in every way typical of the so-called "true Mikulicz's disease." They were symmetric, chronic and painless. The lacrimal glands were first involved, then the parotids and finally the accessory salivary glands, even those on the tip of the tongue, which are so characteristic of the affection. Their hardness to palpation is a feature that has attracted the attention of most observers. Finally, complete agreement is reached in the tendency to spontaneous involution.

Among the hundred or more cases which have been reported under the name Mikulicz's syndrome have been examples of several systemic diseases. Many, of course, were part of a leukemia, and these together with those which are apparently lymphomata with no systemic disease are the cases to which some authors, notably Howard,² have attempted to restrict the name. Three cases of undoubted tuberculosis have been reported (*vide infra*). Several have been found inluetics, as, for example, the cases of de Massary and Tockman³ and Gutmann.⁴ Deglos⁵ has reported an example of the syndrome in a woman of sixty-four with gout. In another interesting group of cases the salivary glands have been enlarged since birth, with similar tumors among other members of the same families (Quinke,⁶ Leri,⁷ and Fontoynt⁸). It is also of interest to note that a bilateral swelling of the salivary glands occurs intermittently, with complete subsidence between attacks in a condition which has been called *sialodochitis fibrinosa*; one of the early cases, that of Battle,⁹ seems to have belonged to this group.

² Bull. et mém. Soc. méd. d. hôp. de Paris, 1918, 3 S., xiii, 627.

³ Berl. klin. Wehnschr., 1907, xlv, 1141.

⁴ Presse méd., Paris, 1912, xx, 125.

⁵ München. med. Wehnschr., 1906, liii, 1, 1213.

⁶ Bull. et mém. Soc. méd. d. hôp. de Paris, 1912, xxxviii, 562.

⁷ Presse méd., Paris, 1911, xix, 455.

⁸ Tr. Clin. Soc., London, 1895, xciii, 282.

Thursfield,¹⁰ in a very exhaustive clinical review, classifies the cases reported as follows:

1. A congenital, hereditary or familial affection.
2. "Mikulicz's disease proper."
3. Mikulicz's disease, with involvement of the lymphatic apparatus.
4. Leukemia.
5. Tuberculosis.
6. Syphilis.
7. Gout.
8. Sialodochitis fibrinosa.

A glance at such a classification shows that one author, at least, allows considerable latitude in the limits which the term may include. We are certainly with the majority of writers in giving the syndrome sufficient breadth to admit such a case as this.

IV. Mikulicz's Disease and Tuberculosis. I have been able to find only three cases of Mikulicz's disease that were undoubtedly tuberculous.

Plitt's case,¹¹ one of the *formes frustes*, was that of a young man with the parotids only involved. He gave a history of tuberculosis earlier in life, the tuberculin reaction was positive and tubercle bacilli were found in the gland. Krailsheimer¹² observed a case with the characteristic bilateral swelling of the salivary and lacrimal glands in whom there was a "catarrhal pulmonary affection;" the tuberculin reaction was positive and the microscopic examination of the extirpated glands was strongly suggestive of tuberculosis. The diagnosis was confirmed by the development of a bilateral typically tuberculous iridocyclitis. The process healed under therapy with new tuberculin. Napp¹³ described a case of undoubted tuberculosis of the salivary and lacrimal glands, with miliary tubercles in the oral and conjunctival mucosæ. Some of the tubercles caseated, and the bacilli were found in the extirpated gland. There was mentioned in his report some pathology of the left pulmonary apex.

In all three of these cases the clinical picture was in harmony with the diagnosis of tuberculosis as made by the microscope. In each case there were some points suggestive of tuberculosis, and at least one which clinched the diagnosis. There are besides these undoubted cases a few more in which a tuberculous etiology is more or less strongly suggested. The patient reported by Osler¹⁵ for instance, had, besides the enlargement of the lacrimal and salivary glands,

¹⁰ Quart. Jour. Med., 1913, vii, 237.

¹¹ von Brunn: Beitr. z. klin. Chir., Tübingen, 1905, xiv, 225.

¹² Beilageheft d. klin. Monatsblat. f. Augenheilk., 1905, xiii, 2, 40.

¹³ Ophth. Klinik, 1907, p. 15.

¹⁴ Ztschr. f. Augenheilk., 1907, xvii, 513.

¹⁵ Am. Jour. Med. Sc., vol. cxv, p. 1893.

pulmonary tuberculosis; however, she had also a rhinitis which was regarded as luetic. In Pick's case,¹⁶ though there was also a bilateral apical tuberculosis with acid-fast bacilli in the sputum, the author was convinced that the microscopic pathology was not that of tuberculosis. Igersheimer and Poellot¹⁷ discuss the various reported cases, and conclude that though tuberculosis does occasionally cause the syndrome of Mikulicz it is an unusual etiology of the condition and that the majority of cases have nothing to do with tuberculosis.

It is to this group of cases that the one herein reported belongs. To attempt to defend the thesis that any large proportion of the cases of Mikulicz's syndrome is atypical tuberculosis would, in the light of our present information on the whole subject, be absurd. It is an interesting possibility, however.

V. Mikulicz's Syndrome and Skin Lesions. Two cases of Mikulicz's disease with cutaneous manifestations have been reported. Neither case was tuberculous. The clinical description of the skin infiltrations and the histologic examination of the extirpated tissue did not suggest it in either case under discussion.

Hackel's patient¹⁸ had enlargement of the lacrimal, parotid and submaxillary glands. He came to autopsy as the result of an ulcerative enteritis. Scattered over the head and back were painful cutaneous tumors the size of beans, with a feeling of tension and heat, and tender to pressure. On the breast were many firm, reddish wheals. There were a few more of these on the back and abdomen. Histologically the skin showed a round-cell infiltration around the sebaceous glands. There was some newformed connective tissue around these islands. The skin infiltrations, the great enlargement of the spleen, the fever, the course of the disease and the histology of the tissues make it seem probable that this was an example of aleukemic leukemia.

Plate and Lewandowsky¹⁹ reported a remarkable case in a twelve-year-old boy, who developed during excellent health painless swellings of the parotid, submaxillary and sublingual glands. The axillary, cervical and inguinal glands were found enlarged and the spleen was palpable. An exanthem appeared on the inner and anterior surfaces of both legs, consisting of many round, ill-defined, painless lesions. They were about the size of a mark, light red in color and slightly elevated. The eruption had the localization, appearance and course of an erythema nodosum. It went through the usual color changes, gradually fading; new lesions appeared and went through the same process, always confined to the legs

¹⁶ Zentralbl. f. Augenheilk., 1896, xx, 97.

¹⁷ Arch. f. Ophthal. v. Graefe, 1910, lxxiv, 411.

¹⁸ Hackel; Arch. f. Chirurgie, 1903, lxi, 1910.

¹⁹ Plate and Lewandowsky; Mitt. aus d. Grenzgeb. d. Med. u. Chir., 1912, xxv, 539.

NOTE.—Extended bibliographies will be found in 2, 10, 11 and 17.

below the knees, except on one occasion, when there were a few lesions on the buttocks. After six months he began to improve and in another half-year had entirely recovered. The authors regard it as a case of chronic infection by an unknown organism. Wassermann and von Pirquet reactions were negative. Examination of a piece of skin from the leg showed a chronic inflammatory reaction, fibroblasts predominating. The infiltration followed the vessels, and was greatest in the vascular regions near the follicles and sweat-glands, being confined to the cutis and subcutis. There were a few epithelioid cells and a few polynuclear cells, though no real giant cells. Tubercle bacilli could not be found.

That these two cases do not suggest in any way the one herein reported is obvious and the three cannot be grouped together except as cases of Mikulicz's syndrome with skin lesions. Our case is the only one of the three in which we can say definitely what these lesions are.

VI. Summary. 1. An unusual case of tuberculosis is presented, in which there is a typical clinical picture of Mikulicz's syndrome associated with atypical pulmonary and cutaneous lesions. Histologic examination of a salivary gland and of a subcutaneous tumor reveals undoubted miliary tubercles.

2. Search of the literature reveals only three other cases of the syndrome which are beyond question tuberculous, and only two other cases with skin manifestations, neither of which resembles this one.

In conclusion, I wish to thank Dr. L. H. Newburgh for his kind and valuable suggestions in the study of the case and the preparation of this report.

SYPHILIS OF THE TRACHEA AND BRONCHI: A RESUME OF THE DIAGNOSTIC FEATURES, WITH THREE CASE REPORTS.

By PHILIP MOEN STIMSON, M.D.,

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WHEN syphilitic lesions occur in the trachea and bronchi the resulting clinical picture, though somewhat variable, usually has certain definite features so characteristic that the diagnosis can be made by means of a careful study of the history and the physical examination of the patient without laboratory assistance. The purpose of this paper is (1) to state briefly what these characteristic features are, and (2) to present the case reports of two cases seen within four months of each other on the service of Dr. L. A. Conner, the first medical division of the New York Hospital, and also an abstract from the record of a third case on the same division three years before.

Conner's monograph¹ on this subject (1903) has remained authoritative. He divides the syphilitic lesions of the trachea and bronchi into four main types:

1. Gummatous swellings—circumscribed or diffuse.
2. Ulcers—single or multiple and with all possible variations.
3. Endotracheal connective-tissue new growth:
 - (a) Distinct scars.
 - (b) Diffuse thickening.
4. Fibrous peritracheitis, *i. e.*, masses of dense fibrous tissue developing outside the cartilaginous rings.

Associated lesions are those of syphilis in the larynx and higher air passages, and in the lungs, those of the various pneumonias, dilatation of the trachea and bronchi, etc.

The affection is commonest in the fourth decade and is slightly more frequent among men than among women. The duration of the syphilitic infection varies enormously, that is, from nine months to forty-two years. The lesions may be due to congenital syphilis. The rarity of the occurrence of syphilitic lesions in the trachea and bronchi is shown by Symmers² in his report on the syphilitic lesions found in 4880 necropsies. Although there was anatomic confirmation of the existence of syphilis in 314 cases, or 6.5 per cent., Symmers found syphilitic lesions of the trachea in only 4 cases, that is, in slightly over 1 per cent. of the syphilitic cases and in less than 1 in 1000 of all cases. He does not report finding syphilitic lesions in the bronchi. On the other hand, C. Jackson³ has written that of the specific inflammations that may cause tracheal stenosis, *viz.*, syphilis, tuberculosis, glanders, typhoid fever and diphtheria, syphilis is by far the most frequent cause, in first its edematous stage and later in its cicatricial stage. And Howard⁴ has said in a discussion of bronchiectasis that the possibility of syphilitic stenosis must always be excluded as an etiologic factor. In any case the diagnosis is important because of the gravity of the symptoms and the likelihood of cure by appropriate treatment, for without such treatment the prognosis is quite bad, over half of Conner's series of collected cases being fatal.

Symptomatology. The stages are commonly those of tracheal or bronchial obstruction. Gerhardt⁵ noted three stages:

¹ L. A. Conner: Syphilis of the Trachea and Bronchi, *AM JOUR. MED. SC.*, July, 1903, cxxv, 57.

² Anatomic Lesions in Late Acquired Syphilis, *Jour. Am. Med. Assn.*, May, 6, 1916, lxvi, 1457.

³ Tracheobronchoscopy, Esophagoscopy and Gastroscopy, p. 43. Pub. by The Laryngoscope Co., St. Louis, Mo., 1907.

⁴ C. P. Howard: The Etiology and Pathogenesis of Bronchiectasis, *AM. JOUR. MED. SC.*, March, 1914, cxlvii, 313.

⁵ Gerhardt: Quoted by Conner, *Deutsch. Arch. f. klin. Med.*, 1867, Bd. ii, 535. Also Osler and Gibson: Syphilis of the Trachea and Bronchi, in *Section on Visceral Syphilis, System of Syphilis*, Oxford Med. Pubs., 1914, iii, 7. S. Israel: Syphilis of the Tracheobronchial Tree; Case of Gumma of Trachea, *Texas State Jour. of Med.*, February, 1920, xv, 362; also abstr. in *Jour. Am. Med. Assn.*, March 13, 1920, lxxiv, 765.

1. Stage of irritation.
2. Stage of permanent stenosis.
3. Stage of suffocating attacks.

As to the earliest symptom, cough is often the first, indicating the stage of irritation, that is before obstruction comes on. Sometimes dyspnea has been the first symptom or the two have appeared together. Quite usually the history is of less than one year's duration.

Of individual symptoms, cough is a prominent one, as well as often the earliest, and though quite variable it usually has a brassy, ringing quality similar to that heard with compression or irritation of the trachea in cases of aneurysm of the arch of the aorta. This quality is characteristic and is of importance in the diagnosis. The sputum is variable in amount and character. Hemorrhage once in a while is profuse, but more frequently only sufficient blood is raised to streak the sputum. Of all the symptoms, dyspnea is perhaps the most constant and most conspicuous, usually beginning early and increasing in severity to occupy the foreground of an extremely alarming and distressing clinical picture. It appears in two distinct forms: a constant dyspnea and paroxysms. The constant dyspnea is continuous and progressive, indicating the stage of permanent stenosis. The paroxysmal form is characterized by superimposed attacks of alarming air hunger, with orthopnea; cyanosis; stridor; inspiratory sinking-in of the tissues of the neck and epigastrium; rapid, feeble pulse and sometimes even unconsciousness. This form, demarking the stage of suffocative attacks, occurs in about half the cases, and death may occur during such an attack. Stridor is a very conspicuous and striking symptom. It may occur during either inspiration alone or expiration alone, or during both. Its character and intensity are quite variable in different cases. Pain is not often a conspicuous symptom, and, when present, does not by its location assist materially in locating the lesion. Tenderness is mentioned in descriptions of tracheobronchial syphilis but is relatively unimportant. The voice, even with an apparently normal larynx, may assume almost any abnormal character or even disappear. A marked limitation in the vertical mobility of the larynx during respiration is considered of considerable diagnostic importance, particularly in differentiating tracheal stenosis from laryngeal stenosis. Lung signs and conditions are very variable and are often concealed by the stridor or by tracheal rhonchi.

The diagnostic difficulties vary according as to whether there are or are not signs of obstruction to breathing. If there are not the diagnosis is usually made by actually seeing the lesion as in a bronchoscopic examination and by blood Wassermann tests, etc., the symptoms—cough, pain, sputum, etc.—being common to various pulmonary conditions. But obstruction in the larger air passages usually gives a characteristic and unmistakable clinical picture, the features of this being (1) a peculiar type of dyspneic breathing, in

which the prolonged, labored and relatively slow inspiration and the shorter easy expiration follow each other without the usual pauses; (2) a stridulous sound chiefly or altogether inspiratory; (3) a characteristic hard, brassy cough, often paroxysmal; (4) in most cases an inspiratory sinking-in of the tissues of the root of the neck, the epigastrium and the lower intercostal spaces. Laryngeal examination will rule out laryngeal obstruction, but if such an examination is impossible for some reason or other, points that may help in differentiating laryngeal from tracheal or bronchial obstruction may be obtained from a careful study of the history, the character of the voice, the amount of respiratory movement of the larynx, the location of the inspiratory thrill and the point of greatest intensity of the stridor, and possible variation in the signs over the two sides of the chest.

Non-syphilitic causes of tracheobronchial stenosis must be ruled out if possible. Of the non-luetic conditions causing compression of the trachea or bronchi from without, one must consider goiter, enlarged lymph glands, as in tuberculosis or in Hodgkin's disease, thoracic aneurysm, neoplasms, etc. Possible factors operating from within to cause obstruction include foreign bodies, simple and malignant new growths and other, very rare, conditions.

The reports of the three cases follow:

CASE I.—H. W., female, aged thirty years, single, no occupation, was admitted December 10, 1915, the chief complaints on admission being of paroxysmal attacks of coughing, with suffocating dyspnea and a "rapid heart."

History. The family history was irrelevant and showed nothing to indicate the presence of congenital lues. The patient had had diphtheria at five and so-called "rheumatism" at eight, but otherwise had never been ill before and had had no previous illnesses like the present trouble. She was accustomed to six to eight alcoholic drinks a day.

Present Illness. Paroxysmal attacks of coughing started three and a half months prior to admission and continued, with increasing severity, up to the time of admission. At first the attacks came on only in the early morning, and after coughing and vomiting the patient would feel well for the rest of the day. This condition lasted about three weeks and then for two weeks stopped practically entirely; but then the attacks became much more severe, so that for the five or six weeks before admission she coughed all day and seemed unable to get her breath, "occasionally becoming somewhat blue in the face." Six days before admission the cough became even more severe and more paroxysmal in character, the breathing more labored and her face markedly cyanotic. This condition persisted up to the time of her admission. There were no chills nor headaches.

Her average weight had been 138 pounds, but at the time of admission she weighed only 110 pounds.

Physical Examination on Admission. The patient is a fairly well-nourished, white woman, aged thirty years, sitting propped up in bed, apparently acutely ill. Respirations are increased in rate (about thirty-eight per minute) and markedly stridulous in character, the stridor being "so near the ear as almost to make it seem to have come from the larynx," and there are loud asthmatic wheezes to be heard. Occasionally the patient is seized with a paroxysm of violent coughing, the cough being distinctly brassy and ringing in character. During these paroxysms she becomes very markedly cyanotic, but even in the intervals she is continually quite cyanotic. The respiratory effort is great, both on inspiration and expiration.

Head. The pupils are moderate in size, regular, equal and active; the ocular movements are normal. The lips are cyanotic. The teeth are in good condition, but with a small focus of pyorrhea. The tongue is moist and considerably coated. The tonsils and pharynx are negative. There are no ulcerations on the mucous membranes.

The lymph glands are small; the epitrochlears are not palpable. The neck reveals no rigidity nor abnormal masses; there was no thyroid enlargement.

The chest is symmetrical and well formed. The respiratory movement on the left side is definitely less than that on the right. The percussion note is normal throughout the lungs, with slight dulness over the right apex, the change, however, being well within the limits of normal. There are loud and wheezy, sonorous and sibilant rales, typically asthmatic in character, throughout both lungs; but the transmission of these rales or rhonchi and of the vesicular element of the breath sounds is distinctly less to the left side than it is to the right. The voice sounds seem alike on the two sides. There is no palpable cardiac impulse. The area of dulness extends from 8.5 cm. out in the fifth left interspace to the right border of the sternum. The heart sounds are markedly obscured but apparently normal in character. The *pulses* are moderate in volume and tension; regular in force and rhythm, and alike in the two wrists.

The abdomen reveals no tenderness, no masses nor rigidity. There are normal limits to the liver dulness and the liver edge is not felt. There are no scars, edema nor tenderness along the tibiae. A fine tremor is present in the fingers of the outstretched hands. The knee-jerks are normal. The abdominal reflexes are absent.

Summary. There is marked stridulous, wheezy respiration, with paroxysms of brassy coughing, and marked cyanosis. The respiratory movement is greater on the right side than on the left. The transmission of asthmatic rhonchi and of the breath sounds is greater to the right side than to the left. No luetic stigmata are found.

Course in Hospital. (Excerpt from discharge note).

"On admission she presented a greatly weakened condition, with marked difficulty in stridulous breathing. Examination of the chest was negative except for lessened respiratory movement on the left side and poorer transmission of breath sounds on that side. Laryngeal obstruction was ruled out by examination. In the absence of all signs of aneurysm or of mediastinal growth, a diagnosis of lues of the left bronchus, with obstruction, was made by Dr. Conner and an immediate blood Wassermann taken; however, because of the urgency of the symptoms, the patient was given mercury without waiting for the result of the Wassermann. That, however, was found to be positive a few hours later, and on the next day (second day in the hospital) she received 0.3 gm. of salvarsan; her symptoms on this day were much relieved, though she began to express delusional ideas, which were considered part of an exhaustive psychosis. Her temperature had fallen and her pulse had become slower and of much better quality. However, on the following day (the twelfth) she developed a high fever; and on the second day of the same, signs of consolidation were found over the right lower lobe. From that time on she lost strength and died from exhaustion December 17, 1915, at 1 A.M., without the breathing at any time returning to the character it had on admission."

SPECIAL EXAMINATIONS.

Blood counts.	On admission, Dec. 10, 1915.	Dec. 15, 1915.
White blood cells	15,000	29,000
Hemoglobin (Sahli)	90 per cent.
Polymorphonuclears	82 per cent.	85 "
Small lymphocytes	13 "	8 "
Large mononuclears	3 "	2 "
Transitionals	2 "	5 "

Wassermann (blood), December 10, 1915, + + + + (maximum).

Urine analyses, essentially negative.

Blood-pressure, on admission, right arm: systolic, 120; diastolic, 80; left arm: systolic, 115; diastolic, 80.

Autopsy. December 17, 1915 (Dr. Elser), eleven hours post mortem: Abstract from the report.

Diagnoses:—Syphilis.

(Gumma of bronchial and mediastinal lymph nodes).

(Gumma of liver, Hepar Lobatum).

Stenosis of left bronchus (partial obstruction).

(Stenosis of left branch of pulmonary artery).

Chronic parenchymatous nephritis.

Lobar pneumonia.

Inspection. Body small but otherwise fairly well developed and fairly well-nourished female. An external examination reveals no evidences of syphilis.

Pleura. Pleura free from adhesions. The visceral layer of the pleura over the lower lobe on both sides is covered with a recent fibrinous exudate.

Thymus. The thymus is absent. The mediastinum is definitely fuller than usual and the contained structures are firmer.

Pericardium. Pericardium smooth and glistening throughout. Contains about 20 c.c. of clear serous fluid.

Heart. The heart is normal in size. The left chambers contain a small amount of clotted blood. The right chambers are filled with a chicken clot and are normal in size. The valves are normal throughout (no evidences of relative insufficiency on the right side). Myocardium is grayish pink in color, opaque in appearance and rather flabby in consistence. No focal lesions. The pulmonary artery was opened and the finger passed up into the two branches of this vessel. The right branch of this vessel permitted the passage of the index finger, while the finger passed into the left branch meets with a definite constriction at a point corresponding to the entrance of this vessel into the lung. At this point the vessel permits the entrance of the tip of the little finger only and the posterior wall of the vessel on the cardiac side of the constriction is puckered, suggesting that the stenosis is due to the contraction of tissues situated behind this vessel.

The lungs, heart, mediastinal structures, trachea, larynx and tongue were removed intact and the subsequent dissection reveals the following:

The faucial and lingual tonsils were normal. The tongue showed no evidences of syphilis. The median glosso-epiglottidean ligament is slightly thickened and retracted, causing a more marked anterior curvature of the epiglottis than is usual (syphilis?). The larynx and trachea apart from congestion of the mucosa present nothing unusual. Thyroid is normal in size and appearance. The deep cervical nodes are moderately swollen and congested. The nodes along the trachea as it enters the thorax are also moderately enlarged and some of them definitely indurated. Cut section of one of these nodes shows that it is partly replaced by a nodule having the typical appearances and consistency (elastic) of a gumma. The superficial mediastinal nodes are swollen and congested; the deeper nodes at the bifurcation of the trachea and at the hilum of both lungs are enlarged and indurated. A dissection of these nodes was not made (specimen preserved for museum purposes). The right bronchus and its main branches were opened by an incision along the posterior wall. On the anterior wall of the right bronchus just below the point of bifurcation of the trachea an irregularly circular defect about 1 cm. in diameter was found. The margins of this ulcer showed a thin gray slough while the base was formed by an indurated and anthracotic lymph node. The wall of the left bronchus showed an extensive irregular defect involving the lower surface of this tube. Projecting

through this opening into the lumen of the bronchus there was a soft node about the size of a small lima bean. This body was evidently responsible for the symptoms of stenosis observed during the life of the patient. The margins of this ulcer were ragged and covered by a thin gray slough. The bronchial mucosa was deeply congested throughout. Transection of one of the larger indurated bronchial nodes showed that it was completely replaced by a gummatous growth which because of the edema of the tissues had lost some of its characteristic features (appearance and consistency).

Lungs. The lower lobes on both sides with the exception of the apices and a few areas in the lowermost portions of these lobes were consolidated. Cut section shows the typical uniformly granular gray and reddish gray appearances of a frank lobar pneumonia. The uninvolved portions of the lower lobes and the upper lobes (including the middle lobe) were edematous and congested.

Liver. Liver larger than normal. Weight, 3 pounds 14 ounces. The upper surface of the right lobe is covered by adhesions. The right lobe shows a number of deep scars dividing this portion of the organ up into a number of smaller lobes (hepar lobatum). Cut section of these scars reveals gummatous deposits. The liver as a whole shows a moderate grade of congestion with a high grade of fatty infiltration. No microscopic evidences of a diffuse cirrhosis.

Gastro-intestinal Tract. Esophagus normal. Stomach normal in size. The remainder of the intestinal tract presents nothing unusual. Solitary and agminated follicles normal. Appendix normal. Mesenteric nodes present nothing unusual.

Aorta. Normal throughout.

Microscopic Examination. The lymph nodes show the lesions of a gumma.

CASE II.—A. J. C., male, aged forty years, married, a salesman, was referred by Dr. Josph L. Frey, and admitted March 28, 1916, complaining of a paroxysmal cough and noisy, difficult breathing of about three years' duration.

History. The family history was unimportant and gave no indication of congenital lues. The patient had pleurisy without effusion in the right chest seven years before admission, and has had occasional "colds." Two years before admission, following ten to fifteen years of difficulty in breathing through his nose, he had a nasal polyp removed from the right side and was relieved. Section and study of the tissue removed was not done. As a salesman he has had to do much talking, and at times has had a husky voice and sore-throat in consequence. He admits two Neisser infections but denies luetic infection by name and symptom. A first wife's only two pregnancies ended in stillbirths, but a second wife has had three normal pregnancies only. He occasionally drinks three or four whiskys a day, but frequently none at all.

Present Illness. The first symptom noticed was about three years before admission, when the patient noticed the gradual onset of an occasional cough. At first the cough was harsh and tearing in character and practically unproductive. Later it seemed to him to sound "hollower." He was usually freer from the cough during the summer months, but during the winters the cough became progressively worse and was most severe about ten days before admission. Even during the winter months, however, he occasionally had short periods in which he was comparatively free from the cough, and during the week before admission he was better than during the week before that. Occasionally with the cough he would have a great deal of difficulty with breathing, and about eight times during the past twelve months he has had paroxysms of coughing so severe as to be terminated by syncope for a brief time, even falling off a chair and completely "losing his bearings." His friends have told him that he would become red at these times but not particularly blue. These paroxysms occurred at no particular hour and without apparent cause or exciting factor.

Five or six months after the cough began the patient began to have a good deal of dyspnea on exertion, but not usually when sitting still, except on wet days. This was considered to be asthma by a doctor. Also, for the past two years, he has been unable to sleep in a horizontal position because of the cough. For two years he has been able to hear himself breathe, both during inspiration and expiration, and friends have commented on it for a year.

He has had some expectoration for two and a half years, but especially for the past year. The amount of sputum has varied from none after much coughing to a mouthful. There has been no profuse expectoration on arising in the morning. The sputum has usually been a yellowish-white mucus, occasionally streaked with blood, and with no particularly offensive odor and no hemorrhage as such. During the past two or three months he has frequently felt as though there was some sticky adherent mucus in his trachea, because at these times he would breathe with difficulty and in an unusually noisy and wheezing manner, and on these occasions he would expectorate rather profusely.

He has had no chest pains at any time, but occasionally has a sensation of compression. He has had no headaches and has not slept well because of the coughing.

Physical Examination on Admission. The patient is a muscular, well-nourished man, aged forty years, lying comfortably in bed and does not appear to be acutely ill. There is no cyanosis. A moderate cough is present, characterized by a peculiar deep barking sound and productive of a rather considerable amount of whitish sputum showing a few pink streaks.

The pupils are equal, regular and react to light and accommodation. The pharynx shows a mild chronic pharyngitis, but there

are no evidences of palatal paralysis nor signs of any growth, nor are there any scars nor mucous patches. The cervical veins are not engorged and no abnormal pulsations are made out in the neck.

The chest is symmetrical, large and muscular. Respirations are slightly increased in rate and inspiration and expiration are apparently of equal length. During both the breath sounds are audible as coarse, moist sounds, apparently in the throat. Expansion is good and apparently equal on the two sides. In the left chest anteriorly the wheeze of the breath sounds is distinctly palpable during both inspiration and expiration. This is also true in the left chest posteriorly and to a lesser extent in the right chest posteriorly but it is not felt in the right chest anteriorly. Tactile fremitus is apparently equally transmitted throughout both lungs. Resonance is slightly decreased throughout both lungs, probably due to the thickness of the chest wall and the muscular development. No special areas of dulness or hyperresonance are made out. In the left chest anteriorly the breath sounds are entirely obscured by coarse, squeaking, loud rhonchi, which are of equal length in inspiration and expiration and which are also similarly heard in the left chest posteriorly. In the right lung anteriorly the breath sounds can be made out as vesicular and well transmitted, but moderately obscured by similar rhonchi of lesser intensity and loudness; so also in the right chest posteriorly. No rales are heard. Whispered and spoken voice sounds are equally and moderately well transmitted throughout both lungs.

Heart. There is very little if any palpable impulse and the apex beat is not localized. The area of relative cardiac dulness lies entirely between the sternum and 10 cm. out in the fourth left interspace and the area of absolute dulness is quite small. The heart action is rather slow and regular. The second pulmonic sound is not augmented. The sounds are of good quality and no murmurs are heard.

The abdomen is negative. The liver dulness extends from the upper border of the fifth rib to the costal margin. The lymph glands are not enlarged; the epitrochlears are not palpable. The external genitalia are normal. The extremities are normal; the knee-jerks are equal and active. The skin is smooth and moist; normal in color; and no scars or eruptions are present. There are no enlarged or prominent veins on the chest.

Course in Hospital. March 28, 1916, admitted. Temperature, 100.8°; pulse, 112; respirations, 24; blood-pressure, 120.

Examination of larynx by Dr. Erskine:

"Epiglottis V-shaped. Signs of a mild chronic laryngitis; viz., cords slightly pink and slightly thicker at the free edge than normal. No paralysis. No signs of any growth. No scars in pharynx. No mucous patches seen."

Wassermann (blood): "Must go in the doubtful class. Circumstances required performance of the test by the incubation method and a repeat Wassermann was asked for."

March 29. Roentgen ray: Site examined, chest. "Enlarged glands in mediastinum and appearance of slight displacement of aorta to left."

Urine: Negative for albumin, sugar and casts.

*March 30. Bronchoscopic Examination by Dr. H. Arrowsmith.**
(Local Anesthesia.)

"Both vocal bands are considerably thickened and very decidedly congested and their free edges are very uneven, showing almost a condition of serration. The tracheal mucous membrane is uniformly congested and thickened.

About one inch above the carina on the posterior tracheal wall is an irregular, apparently fungating mass, perhaps the size of a marrow-fat pea. (Specimen removed for examination—see report under April 5.) There was rather more respiratory movement in the trachea than is ordinarily seen. Tentative Diagnosis: Gumma of the Trachea."

Sputum. Negative for tubercle bacilli.

Second Blood Wassermann. Frankly positive.

Blood Count. Hemoglobin, 90 per cent. White blood cells, 12,200; polynuclears, 65; transitionals, 7; lymphocytes, 13; large mononuclears, 10; eosinophiles, 5.

April 1. 0.6 gm. arsenobenzol given intravenously.

April 2. Temperature reaction up to 102.4° from average of 100°.

Sputum. Quantity in twenty-four hours, 4 ounces.

Clinical Note. "Patient's general and local conditions seem to have improved considerably; he feels better; sleeps better; coughs less frequently and with less of the low-pitched barking quality; and the amount of sputum raised is less. He complains a little of pains behind his shoulders when he lies on his side. These pains have appeared since the injection of arsenobenzol."

Sputum. Amount 3 ounces.

April 4. Temperature, 100°.

Clinical Note. "In the left lung the vesicular murmur of the breath sounds can be readily distinguished, the rhonchi having markedly cleared up."

Mercury salicylate, gm. 1, given intramuscularly.

Sputum. Amount 4 ounces.

April 5. Pathologic report on the tissue removed during the bronchoscopic examination:

* Since this examination Arrowsmith (*Tracheobronchial Syphilis*, New York Med. Jour., June 24, 1916, cii, 1211) has published an article on tracheobronchial syphilis in which he comments on the paucity of the literature on the subject and describes in detail a case he had seen in Brooklyn in which his bronchoscopic diagnosis was "diffuse indurative peritracheobronchitis with stenosis." He also mentions this examination.

“**Diagnosis.** Chronic inflammation of bronchial mucosa of unknown origin.

“Specimen consists of a single bit of tissue, the size of a pin’s head, snared from the bronchus with bronchial forceps.

“**Microscopic Examination.** The sections of the material received show it to be a bit of mucous membrane apparently covered with stratified columnar epithelium. No mucous glands are present in the sections. There is considerable hemorrhagic round-celled and plasma-celled infiltration of the submucosa, but very few polynuclear leukocytes being seen. There are also some evidences of necrosis but none of tuberculosis, nor of malignant process. While the diagnosis of ‘syphilis’ cannot be made on the microscopic findings there is nothing in the sections that would contra-indicate it.”

April 5-8. Sputum. Amount, 2 ounces a day.

April 7. Clinical Note. “Patient’s cough has lost almost all of its deep characteristic barking character.”

Arsenobenzol. 0.6 gm. given intravenously.

Temperature. Average 99.5°.

April 8. Temperature reaction 102°.

April 9. Mercury salicylate, 1 gm. given intramuscularly.
Sputum. Amount 1 ounce.

April 12. Sputum. Amount $\frac{1}{2}$ ounce.

Patient allowed to go home.

Discharge Note. “This is the second case of syphilis of the trachea and bronchi to appear on the division within four months. This man’s history of paroxysmal attacks of coughing, his stridulous breathing and his peculiar, deep, barking cough furnished Dr. Conner sufficient grounds for a fairly definite diagnosis of ‘syphilis of the trachea.’ A first blood Wassermann was reported as indefinite, but a second was strongly positive. Bronchoscopy revealed a small papule just above the carina, section of which showed round-celled and plasma-celled infiltration of chronic inflammatory tissue—not pathognomonic of any certain condition, but at least not contra-indicating syphilis. Active antisymphilitic treatment was started with arsenobenzol and mercury, with marked and early diminution in the severity and frequency of the cough, decrease in the amount of sputum and a pronounced increase in the patient’s sense of general well-being. Patient now returns to his own doctor, Dr. Frey, for further antiluetic treatment.

Diagnosis. Syphilis of the trachea.

Result. Improved.”

May 7. The patient called at the hospital. “He has had two more doses of arsenobenzol from Dr. Frey, also mercury and iodides. His voice is clearer and he feels much better. There is practically no dyspnea even on exertion, and he can sleep prone. The expansion is apparently equal on the two sides, and the breath and voice sounds are equally well transmitted to the two sides. There are a few

rhonchi on the right side. The patient still coughs quite frequently but expectorates very little. The sputum is no longer blood-streaked."

June 14. The patient again called at the hospital. "He has had one more dose of arsenobenzol, also mercury and iodides. The sense of general well-being continues to improve. All symptoms are less marked."

February 1917. Dr. Conner heard that the patient was in good health and at work, although he still had a troublesome cough at times.

July 9, 1920. Dr. Frey, over the telephone, said that the patient had been critically ill in 1918 with an influenzal pneumonia but survived and is now quite well, though still with the occasional troublesome cough. He believes that the patient, who moved out of town, has had no antiluetic treatment since the summer of 1916.

CASE III.—L. B., female, aged thirty-three years, married, was admitted at 3 A.M., April 11, 1913, the chief complaint being dyspnea.

History. There was no history indicative of congenital or acquired syphilis. She had been married eight years but had never been pregnant. Six years before admission she had a mild "rheumatic attack" characterized by low fever and mild polyarticular joint pains, the joints being slightly swollen but not red. She was sick two weeks and made a perfect recovery.

The present illness began with the first of a series of severe attacks of "bronchitis" about one year before admission. This first attack lasted two weeks, confining her to her bed, and was followed by four or five more attacks, each lasting three or four days, and the last attack occurring about two months before admission. During these bronchitis attacks expectoration was very profuse, at times green, at other times dark brown; and frequently it showed quite a little fresh blood. The cough was paroxysmal and hacking, the paroxysms being frequent and lasting for some minutes, so that the patient would become very cyanotic and extremely prostrated. The patient was somewhat short of breath on exertion during the entire two years before admission, but more marked respiratory distress came on during the last three or four days of the first attack of so-called bronchitis and persisted, the patient at no time becoming entirely free from it. This distress consisted of difficulty in both inspiring and expiring, and at times her respirations became exceedingly difficult and painful, being also accompanied by a sensation of weight and downward dragging beneath the sternum. These exacerbations varied from a few hours' duration to that of three or four days, and occurred every three or four weeks. During these severe attacks of dyspnea her breathing was better when she was in a sitting position, but at other times position seemed to make no difference in her breathing, nor was there any variation with the

time of day. Five days before admission, on her way from Texas to New York City, she was forced to stop in St. Louis because of one of these severe attacks of dyspnea, which lasted about four hours. From then until admission the patient had a continuous but rather less severe difficulty in breathing.

During the year's duration of her illness the patient lost between forty and fifty pounds in weight, and no longer had the strength to be up and around. But apart from her respiratory troubles and her attacks of "bronchitis" she was troubled by no other symptoms except an increasing anorexia and weakness.

Physical Examination on Admission. The patient was an emaciated woman, aged thirty-three years, of slender frame and with gray hair. The skin was very pale and the mucous membranes were also pale and slightly cyanotic. The pupils were contracted, regular and showed a slight reaction to light. The eye-grounds were negative, showing no hemorrhages or exudate or choking of the disk. There was no scleral jaundice. The mouth was normal except for a dry and coated tongue. A laryngoscopic examination showed that the vocal cords were symmetrical and widely separated, but they were not seen to move; no growth or other pathologic process was seen in the examination. ("Urgent dyspnea did not allow protracted examination.") The neck showed swollen veins and marked contractions of the accessory muscles of inspiration. The chin was held constantly in a somewhat elevated position. The chest was narrow but "of fair form." The breasts were normal.

There was marked inspiratory and expiratory dyspnea, the former being the more marked, but both being accompanied by a loud stridor, chiefly inspiratory, however. During inspiration, which was somewhat prolonged, there was rapid descent of the diaphragm, and action of all the accessory respiratory muscles, following which there was a marked sinking-in of the intercostal spaces, which in turn was followed by expansion of the chest. Expiration was also forced, the abdominal muscles being boardlike during this phase. During both phases of respiration, but especially during inspiration, a thrill could be felt over the larynx, trachea and left chest, but not over the right chest. Resonance over the lungs was normal throughout, and there was also resonance over the manubrium sterni and over the dorsal spine down to the fourth thoracic vertebra. Breath sounds were vesicular in character and well heard over both lungs, but were louder on the left side. Over the large bronchi on both sides, but especially on the left side, a coarse stridor was heard, increasing in intensity to the larynx, where it was loudest. The thrill of the stridor was felt over the left lung only. Over both lungs expiration was accompanied by sibilant and occasional sonorous rales, and expiration was greatly prolonged, but these sounds were not so intense nor so numerous as in ordinary asthmatic breathing.

The *pulses* were equal, regular, rapid, of poor force and low tension,

and there was no appreciable arterial sclerosis. As to the *heart*, the area of relative dulness extended from the right sternal margin to 10.5 cm. from the midline in the fifth left interspace. The first heart sound at the apex had poor muscular quality while the second sound at that point was described as booming. At the base the second sound at the aortic area was slightly accentuated and was louder than the second pulmonic sound. No murmurs were heard.

The *abdomen* was soft during inspiration and not tender, and no masses were felt other than the liver edge 2 cm. below the right costal margin. The liver dulness began at the fifth rib. The spleen was not felt. The *extremities* showed no edema. There was a small white scar on the inner side of the left patella. The knee-jerks were active and the Babinski test was negative in each foot. *Lymph nodes* were not enlarged.

Course in Hospital. Admitted April 11, 1913, at 3.15 A.M.; temperature, 100°; respirations, 28; pulse, 100.

At the time of admission the patient had a very bad attack, with great difficulty in breathing, but was somewhat relieved by adrenalin. She dozed toward morning and seemed to rest comfortably. During the day and evening she was given several doses of adrenalin and a total of $\frac{2}{3}$ gr. of morphin, and that evening salvarsan 0.3 gm. was given intravenously. That night her breathing seemed much improved and the patient seemed more comfortable, sleeping somewhat. A blood count the following morning (April 12) showed hemoglobin 72 per cent.; white blood cells, 21,000; 93 per cent. polynuclear, and the sputum showed numerous pus cells but no tubercle bacilli. Two uranalyses each showed a trace of albumin and numerous hyaline casts. Blood taken for Wassermann was later reported as giving a positive test. The patient died at 1 P.M. on April 12, her temperature having varied from 101° to 98°; pulse-rate from 92 to 108 except for a terminal 144; and respiration rate from 20 to 32 except for a terminal 42. The terminal temperature was not taken.

No autopsy was performed.

The discharge note reads: "Several times preceding death the patient became almost pulseless, but became stronger following intravenous injections of digipuratum. The muscular effort necessary to maintain respiration was extremely severe. Patient conscious to within an hour of death. A short period of Cheyne-Stokes breathing set in but disappeared soon after camphor in ether was given. The obstruction to respiration did not appear to be greater today than yesterday.

Diagnosis. Syphilis of right bronchus."

The above account of Case No. 3 is based on the hospital records of the case. She was not seen by the present writer.

Summary. In syphilis of the trachea and bronchi the characteristic symptoms are those of tracheal or bronchial obstruction;

that is, (1) a peculiar type of dyspnea with labored, prolonged inspiration and shorter easier expiration; (2) paroxysms of excessive dyspnea, sufficient to cause syncope or even death; (3) cough, which is usually hard, brassy and paroxysmal, though quite variable in character; (4) stridulous sounds, particularly during inspiration; (5) frequently an inspiratory sinking-in of the tissues of the root of the neck, epigastrium and lower intercostal spaces; (6) other features, such as more or less profuse sputum, a limitation in the mobility of the larynx, etc. Wide variations from this symptom-complex, however, are not uncommon.

Case I shows a history in which the principal symptom was a paroxysmal cough of three and a half months' duration and increasing severity, accompanied by dyspnea and cyanosis. The clinical features were paroxysms of coughing, stridor, cyanosis, fever, great effort during both inspiration and expiration, a smaller respiratory movement in the left chest than in the right, numerous rhonchi and rales transmitted more loudly to the right side than to the left and a positive Wassermann, then respiratory relief obtained from mercury and salvarsan, but death soon after from lobar pneumonia. An autopsy revealed a partial obstruction of the left bronchus due to a gummatous lymph node, stenosis of the left pulmonary artery, lobar pneumonia and syphilis.

Case II shows a history of three years of paroxysms of coughing, which for a year were occasionally severe enough to cause syncope. He also had dyspnea, an audible respiration and a moderately profuse expectoration. The clinical features were the peculiar deep barking cough, the stridor, enough dyspnea to make sleeping horizontally difficult, and asthmatic rhonchi in both lungs; also a positive Wassermann, a chronic catarrhal laryngitis and a papule in the lower part of the trachea, after the removal of which and the administration of arsenobenzol there was a steady improvement in the patient's condition.

Case III shows a history of one year of attacks of "bronchitis," with a severe paroxysmal cough and much sputum, also attacks of difficult painful inspiration and expiration, a fairly constant moderate dyspnea and much loss of weight. The clinical features were marked inspiratory and also expiratory dyspnea, notable contractions of the accessory muscles of inspiration, stridor, and inspiratory thrill over the larynx, trachea and left chest, and vesicular breath sounds that were louder on the left side than on the right, also a positive Wassermann, and death thirty-six hours after admission to the hospital. Autopsy was not done. The clinical diagnosis was syphilis of the right bronchus.

I wish to thank Dr. L. A. Conner for permission to publish the accounts of these three cases and for kindly and helpful suggestions as to the form and substance of the article.

REVIEWS

PRINCIPLES OF BIOCHEMISTRY. By T. B. ROBERTSON, PH.D., D.Sc., Professor of Physiology and Biochemistry in the University of Adelaide, South Australia; formerly Professor of Biochemistry in the University of Toronto; Professor of Biochemistry and Pharmacology in the University of California. Pp. 632. Philadelphia and New York: Lea & Febiger.

THAT branch of chemistry which probably possesses the most voluminous literature has the fewest text-books. This is the latest contribution to the field. The *Principles of Biochemistry* is intended for students of medicine, agriculture and related sciences. The range of subjects treated is broad; in addition to the matters one would expect to find discussed in a text-book of biochemistry such subjects as bioluminescence, artificial fertilization and memory also find a place.

As one might expect from the nature of the author's other publications, an effort is made throughout the book to treat biochemistry as an exact science, and mathematical expressions appear much more frequently than in other treatises on the same subject. There is a strong tendency in biochemistry to apply the methods of physical chemistry to life phenomena, and it is well that the task of discussing the subject from this viewpoint has been assumed by one so well prepared to do it. This feature alone makes it a welcome addition to the literature of biochemistry.

The arrangement of the contents is peculiar—perhaps artificial would better describe it. For example, instead of treating alimentary processes as a unit, such closely related topics as the secretion of the digestive enzymes, the actions of these enzymes and the origin of the hydrochloric acid of the gastric juice are described in widely separated places. (The psychic secretion of digestive juices is regarded as physiology and is not discussed.) Vitamines are treated partly in a chapter dealing with nucleic acids and nitrogenous bases because of the assumed chemical composition of these materials, and in another chapter they are mentioned briefly in connection with growth. Their discussion, as a whole, is inadequate in view of the present position of the subject. On the other hand, Robertson's own work on tethelin is considered at length.

Several statements have been noted which outstrip the facts.

On page 193 the hydroxy acids of fruits and vegetables are referred to as antiscorbutics. On page 489 this statement with reference to vitamines occurs: "They evidently represent a group of non-synthesizable essential constituents of living matter which would appear not to be excessively complicated in structure, since they are usually obtainable in crystalline form and their relationship to the pyrimidine and purines has frequently been established."

The chemistry of the simple carbohydrates and of the proteins is so well done as to deserve special mention. R. L. S.

THE PASSING LEGIONS. By GEORGE BUCHANAN FIFE. Pp. 369; 8 illustrations. New York: Macmillan Company.

MR. FIFE has portrayed here, in an interestingly narrative fashion with many amusing anecdotes and stirring tales of human interest, the story of the splendid service rendered by the American Red Cross to the thousands of our soldiers who passed through England *en route* to France, and to our sailors at the American base ports in Great Britain. The book is well worth reading as a side light on our diversified efforts in the war. P. F. W.

HEART AFFECTIONS; THEIR RECOGNITION AND TREATMENT. By S. CALVIN SMITH, M.S., M.D., Instructor in Medicine, University of Pennsylvania Graduate School of Medicine; Visiting Physician to the Philadelphia General Hospital. Pp. 440; 83 illustrations. Philadelphia: F. A. Davis Company.

THE need of a new volume dealing with the disorders of the heart and the bloodvessels does not seem especially to be marked. However, if such a demand exists it is certainly in the demand for a book which deals with the essential elements of cardiac affections and not with the more complicated and advanced studies which have appeared in the last few years. Because of this fact, Dr. Smith has limited his volume very largely to the fundamentals. He describes all that is to be told about the heart and its diseases in language so clear and concise that it can readily be comprehended by a beginner in the field of cardiology.

In general the first two chapters have to do with the elements of cardiac anatomy, physiology and pathology. The succeeding chapters deal with a systematic outline of disorders of the heart and the last three chapters concern cardiac treatment largely. More in detail it may be said that Dr. Smith, in the first portion of the outline of disorders of the heart, takes up the physical examination of

the body, laboratory aids to diagnosis, graphic methods of examination, blood-pressure and so on. He then discusses pathological heart conditions as well as arteriosclerosis and aneurysm. These last two diseases might well have been omitted if the author did not care to discuss them more fully. To neurocirculatory asthenia, a condition which, in its true sense, has no direct relationship with cardiac conditions, is allotted one of the last chapters, while the book closes with an alliterative chapter on "cardiac camouflage." Dr. Smith has prepared his book very carefully. It is not too technical nor too deep for the average practitioner. and should be a great help in teaching him more about cardiac conditions. Sane judgment is used in the description of methods of diagnosis and treatment. A great deal of the author's teaching reflects the sound, good sense of McKenzie and of Lewis, for whom the author apparently has a great admiration.

J. H. M., JR.

THE SCHOOL OF SALERNUM (REGIMEN SANITATIS SALERNITANUM)
The ENGLISH VERSION. By SIR JOHN HARINGTON. Pp. 216;
21 illustrations. New York: Paul B. Hoeber.

PREFACED with a history of the School of Salerno by the editor, Dr. F. R. Packard, and a historical note by Dr. F. H. Garrison, the present edition of this quaint old work is very carefully prepared for new readers. As a medical treatise this book was supposed to have been written for the advice of Robert of Normandy, son of William I of England. Almost numberless copies were made in manuscript in the middle ages, and since the time of printing there have been many editions. Harington's English version was printed in 1607 and was to be sold "at the little shop next Cliffords Inn-gate, in Fleet Streete." The illustrations are taken from early editions of the work. In the *Ad Librum* we are told that then as now, Belgium was devastated by wars. Both English and Latin versions are given and excellent notes complete the book. To all those who are interested in the historical side of medicine this volume will always appeal.

W. H. F. A.

A TEXT-BOOK OF PHYSIOLOGY. FOR STUDENTS AND PRACTITIONERS OF MEDICINE. By RUSSELL BURTON-OPITZ, M.D., PH.D., Associate Professor of Physiology, Columbia University. Pp. 1185; 538 figures. Philadelphia and London: W. B. Saunders Company.

IN this newest American text-book of physiology for students and practitioners of medicine is given the substance of the lectures

which the author has elaborated for his undergraduate classes. The subject is considered in nine parts, of which the longest, containing 192 pages, is devoted to the circulation of the blood, a field in which the author has made special studies. Frequent references to special articles are given in footnotes. These references are mainly to the classical papers on the various topics, although the recent literature is not neglected. The point of view of the author is indicated in the preface, wherein he states that the sole hope of modern medicine is physiology, or, in a larger sense, the experimental sciences. Hence follows the necessity of the student making a conscientious effort to become thoroughly acquainted with this subject. In this book are given all the needful data to accomplish this end. But it would appear at times that the author is a little in doubt as to the student's previous preparation for the task. Mindful of the average person's slowness in correlating the many branches of his knowledge, the author has introduced many brief descriptions in the fields of comparative physiology, histology and embryology as well as physics and chemistry. It is no doubt helpful to give these passing references in the course of systematic lectures, but they seem at times to be unnecessary in a text-book of physiology of this kind. In some of the histological descriptions of organs which are introduced the delineation is so diagrammatic as to present few points of contact with the student's previous instruction. In such cases it would perhaps be more productive of clear thinking to refer the student to the special books on the subject. The volume is well printed and is free from typographical errors. It will doubtless have a wide field of usefulness.

W. H. F. A.

COMMON INFECTIONS OF THE KIDNEYS WITH THE COLON BACILLUS AND ALLIED BACTERIA. By FRANK KIDD, M.B., B.C. (CANTAB.), F.R.C. (ENG.). Surgeon to London Hospital; Surgeon-in-Charge of Genito-Urinary Department, London Hospital; Member of the International Society of Urology, with an additional lecture by DR. PHILIP PANTON, Clinical Pathologist, London Hospital. London: Henry Frowde, Oxford University Press.

THE second book in the series of *Common Diseases* which Mr. Kidd has recently brought forth is an interesting and valuable contribution to the subject of renal infection. The author in the first part of the book discusses blood-born bacterial infections of the kidneys, hematogenous prostatitis, blood-born bacterial infections of the testicle and active hematogenous infections causing spontaneous infection of the bladder. The last chapter in this section is on bacteriology of the urine by Dr. Panton.

These first chapters are well written and instructive, but not nearly as interesting as the chapters in the second section, which

has to do with the theory and the genesis of the various conditions discussed in the first section. The author believes that the body is a bacterial sponge and that the organisms are constantly invading the blood stream, which are soon passed out through the kidney and lungs. If, however, bodily resistance is lowered and the body tissues are not able to handle these organisms we get the various acute and chronic infections in different parts of the body which produce such conditions as rheumatism, lumbago, headache, toxemia and common colds, which the author contends, are nothing more or less than intermittent bacterial infections of the body. In some cases more severe infections are produced and we have the more serious diseases. The author's ideas are interesting and comprehensive, and if he could substantiate his theory we would have a very complete explanation for practically every type of disease to which the body is heir.

J. H. M., JR.

MEDICAL CLINICS OF NORTH AMERICA. St. Louis Number, November, 1920. Philadelphia Number, January, 1921. Philadelphia: W. B. Saunders Company.

THESE interesting medical publications continue in much the same form as heretofore. Various subjects are presented or cases are reported with full discussion which are of interest from some diagnostic, therapeutic or prognostic standpoint. The clinics of these two numbers are for the most part very interesting and are well worth reading. The studies are presented in a more intimate manner than is possible in a text-book, and with less formality than is possible in a medical article, greatly enhancing their readability.

J. H. M., JR.

THE COMMUNITY HEALTH PROBLEM. By ATHEL CAMPBELL BURNHAM, M.D., Health Service, Atlantic Division, American Red Cross; Attending Surgeon, Volunteer Hospital, New York City. Pp. 149. New York: The Macmillan Company.

THE increasing interest in the questions of public health is well exemplified by a number of books relating to various phases of this subject which are now appearing. Thus the latest volume that the reviewer has seen is concerned largely with the question of public health in a local community and deals with such subjects as the private physician in his relation to community health, the health departments in their relation to community health, public health nursing, health centers, industrial medicine and similar subjects. The discussion of these subjects is both sane and logical. The chief

criticism of the book would be in the extreme brevity of the different subjects it discusses, which are touched upon so lightly that one gets but a superficial survey of the broad field of public health measures. After reading the book one has the idea in a general way of what may and can be done in public health, but one is left under the impression that little is said of how it should be done.

J. H. M., JR.

BLOCK ANESTHESIA AND ALLIED SUBJECTS, WITH SPECIAL CHAPTERS ON THE MAXILLARY SINUS, THE TONSILS AND NEURALGIAS OF THE NERVUS TRIGEMINUS. By ARTHUR E. SMITH, D.D.S., M.D., Oral Surgeon to Frances Willard Hospital and to the House of the Good Shepherd, Chicago. Pp. 872; 595 illustrations. St. Louis: C. V. Mosby Company.

THE perfection of synthetic local anesthetics and the improvement in the technic of their administration is such that today a large majority of all operations can be successfully performed without general narcosis. By the block method, local anesthesia has been brought to a degree of perfection which is almost ideal. Its application to the structures of the head and face finds probably its most useful field, and in this complete treatise of the subject, Dr. Smith has furnished for oral surgeons, dentists and laryngologists a text-book of great value.

It is perhaps surprising that it is possible to write a book of some nine hundred pages solely on local anesthesia as applied to the head, but, as in all surgical procedures, it is the attention to details that makes for success, so it is the detail of description and illustration that makes this book of especial merit.

For practical purposes, however, it is possible to have too much elaboration, in that it makes it difficult to grasp the essential points without an unnecessary expenditure of time and effort. In fact, the chief criticism of this book would lie along these lines.

Two very interesting chapters are devoted to the history of anesthesia and its development. The anatomical chapters are very complete, comprising the whole range of the cranial nerves from the histology of a neuron to a detailed description of the terminal anastomoses. It would seem, because of the great amount of space that is devoted to the various methods of anesthetizing the teeth, that the book is especially designed for the use of the dentist; but practically all forms of head surgery, including that of the nose, throat and ear, are completely covered, and with the usual amount of detail, making the book most valuable to the otolaryngologist. There are descriptions of the best methods for producing local anesthesia for mastoid operations, for the removal of goiters, for tonsil and sinus operations and of injections for the relief of the

various neuralgias, and in many cases the author even describes the various operations that the local anesthesia makes possible. The relative value of the different anesthetics has been determined not only from the published statements of others, but also from personal experiments. Their general and local actions and the pathology of the tissues when injected are also carefully considered. In quite a number of the described methods there is considerable originality shown, as, for instance, in the suggested procedure for blocking the sphenopalatine ganglion. It is apparently much simpler and much less pregnant of harm than the classical method of Sluder. Extensively illustrated mostly with photographic reproductions, but also with carefully prepared diagrams and drawings of instruments, we have in this treatise a comprehensive and practical survey of the whole subject of local anesthesia as applied to the head and neck.

We compliment the author on the production of this work and congratulate those surgeons who are privileged to read it.

G. B. W.

PARACELSUS. By J. M. STILLMAN, Professor of Chemistry Emeritus, Stanford University. Pp. 184. Chicago and London: Open Court Publishing Company.

THE reader will find set forth in brief compass a readable and patently authoritative account of the place occupied by Paracelsus in medicine and chemistry. The unbiased viewpoint of the author is evident throughout, and on finishing the book one feels that he has become acquainted with the belligerent, truth-seeking Swiss physician of the sixteenth century about as well as one can at this late date, considering, in addition to the inherent difficulties of such a biographical task, the deliberate falsehoods circulated by Paracelsus' enemies and the extravagant flatteries originated by his disciples.

R. L. S.

PHYSIOLOGICAL CHEMISTRY. By A. P. MATHEWS, Professor of Physiological Chemistry, University of Cincinnati. Pp. 1154. New York: William Wood & Co.

THIS text-book is now so well known that a review is superfluous. The third edition differs from the second chiefly in the enlargement of the practical part. This comprises 268 pages in the present edition instead of 164 in the previous one, and is now comparable with books which are exclusively laboratory guides. The most recent of the methods for the analysis of blood and urine are included. The only important omission noted was the method of Van Slyke for acetone bodies.

R. L. S.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Retinitis of Diabetes Mellitus.—WAGENER and WILDER (*Jour. Am. Med. Assn.*, 1921, lxxvi, 515). Forty-five cases of retinal disease were noted in the course of a study of 300 diabetics at the Mayo Clinic. About 80 of the total number of cases represented were examples of so-called "diabetes gravis," characterized by acute onset of the disease and its progressively increasing severity, and not one of these showed retinal changes. Retinitis occurred exclusively in diabetic patients, with mild, easily controlled glycosuria and in whom evidence of vascular disease was always present. They believe that "the retinitis of diabetes is the retinitis of cardiovascular-renal disease, modified in appearance and in stage of occurrence, possibly by the metabolic disturbances associated with the diabetes."

Immunological Distinctions of Encephalitis and Poliomyelitis.—AMOSS (*Jour. Exp. Med.*, 1921, xxxiii, 187). The author recalls that some observers believe encephalitis and poliomyelitis to be manifestations of the same disease, and that many have noted points of similarity. He summarizes the main differences existing between these two diseases as follows: (1) In lethargic encephalitis the clinical manifestations depend in the main on basal ganglion lesions; in poliomyelitis the main lesions occur in the gray matter of the spinal cord and medulla oblongata. (2) The tendency for poliomyelitis to occur in the summer and autumn months and for lethargic encephalitis to occur in the winter and spring months. (3) Differences in communicability of the disease to monkeys. Poliomyelitis is transmitted with ease by

inoculating monkeys with affected nervous tissue from man, while it is doubtful whether lethargic encephalitis has ever been so transmitted. The author then applies, as a means of distinguishing the two diseases, protection experiments. Under certain circumstances the blood serum of convalescent poliomyelitis cases neutralizes the virus of poliomyelitis when the latter is injected into monkeys. Blood serum from four convalescent encephalitis cases (fifth week, fourth month, fifth month and fifteenth month) gave no protection to monkeys against subsequent inoculation with the virus of epidemic poliomyelitis. The monkeys (controls) which were protected by serum from a monkey which had had experimental poliomyelitis survived.

Pseudo-polycythemia; Extraordinary Blood Changes in a Patient with Renal Calculus.—HERMAN and LYON (*Annals of Surgery*, 1921, lxxiii, 223). The authors report an unusual case of polycythemia in a patient, aged forty-nine years, coming under observation for renal calculus and pyelitis. The blood showed 11,496,000 red blood cells; hemoglobin, 120 per cent.; and 11,600 white blood cells before operation. No cyanosis, splenomegalia nor other signs of polycythemia were present. Three days after removal of the affected kidney the blood picture showed a remarkable change: red blood cells, 5,504,000; hemoglobin, 108 per cent.; white blood cells, 11,200. Thirteen days after operation the red count and hemoglobin were found to be normal, but there were 242,000 leukocytes, with the following differential formula: Polymorphonuclears, 74 per cent.; small mononuclears, 13 per cent.; large lymphocytes, 4 per cent.; transitionals, 5 per cent.; acidophiles, 4 per cent.; and basophiles, 1 per cent. Four days later the blood examination was reported as follows: Red blood cells, 4,360,000; Hemoglobin, 88 per cent.; white blood cells, 22,800. Differential formula: Polymorphonuclears, 81 per cent.; lymphocytes, 16 per cent.; transitionals, 2 per cent.; acidophiles, 1 per cent. Convalescence from operation was uneventful. One year after operation the blood was found to be normal.

Angina Pectoris; An Electrocardiographic Study.—WILLIUS (*Arch. Int. Med.*, 1921, xxvii, 192). The author studied 155 cases of angina pectoris. Nineteen (12.2 per cent.) had recognizable aortic disease; 2 (1.3 per cent.) had mitral stenosis; 134 (86.5 per cent.) had "indeterminate pathological lesions, granting that we must discard the view of coronary disease accepted as true for many years and revealed at necropsy innumerable times." The author finds it difficult to classify this last group (86.5 per cent.) without utilizing the coronary disease hypothesis as the explanation of their angina. Of the total number (155) 128 were male and 27 were female patients. The greatest number (59) occurred in the sixth decade, 45 occurred in the seventh decade and 34 in the fifth. Seven patients in the series had angina, with no demonstrable objective evidence (including significant electrocardiographic abnormalities) of heart disease. From the study Willius arrives at the following conclusions: "(1) There are no electrocardiographic findings pathognomonic of angina pectoris. (2) Significant *T* wave negativity occurred in one-third of the electrocardiograms (32.9 per cent.) and is an important abnormality. (3) Abnormalities in *T* wave contour affecting both the positive and negative wave are

significant. (4) Abnormal QRS complexes in all derivations of the electrocardiogram occurred in 14.2 per cent. of the records. (5) The cardiac mortality of the entire group was 46.7 per cent., definitely contrasted with the higher mortality of those patients having significant T wave negativity (70.3 per cent.) and abnormal QRS complexes in all derivations (62.5 per cent.) of their electrocardiograms."

SURGERY

UNDER THE CHARGE OF

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Multiple Polyposis of the Intestinal Tract.—STRUTHERS (*Annals of Surgery*, 1920, lxxii, vi, 849) says that multiple polyposis of the intestinal tract is a serious disease from the standpoint of morbidity and mortality. The etiology of the intestinal polypus is not known, although chronic ulcerative colitis and intestinal infections appear to be factors. There is no specific medical treatment and operation undoubtedly offers the best results in the more advanced cases. The rectum, the sigmoid, and the splenic and hepatic flexures are most frequently involved. The small intestines are rarely involved. The predominant symptoms are diarrhea, with the passage of pus and blood, vague abdominal pain, and rectal tenesmus. The so-called essential hemorrhage, if present, is almost pathognomonic. Proctoscopic examination should be done routinely in all cases of dysentery. Adenomas do not seem to become malignant more often than polypi and papillomas. In cases in which polypi were associated with carcinoma, they were usually found below the cancerous growth farther along in the intestinal tract. Most marked involvement of the colon is found in the cases which begin as a mild diarrhea and later become chronic. The more sudden and severe the onset the more localized the condition in the colon. Multiple polyposis of the intestinal tract is more frequent in males than in females, a proportion of 2 to 1.

Persistence of Pyloric and Duodenal Ulcers Following Simple Suture of an Acute Perforation.—LEWISOHN (*Annals of Surgery*, 1920, lxxii, v, 595) says that immediate gastro-enterostomy in the treatment of perforated pyloric and duodenal ulcers does not increase the mortality. Gastro-enterostomy and pyloric exclusion simplifies the postoperative treatment considerably. Simple closure of the perforation will not cause a cure of the ulcer in a considerable number of cases. Gastro-enterostomy will guarantee proper drainage of the stomach contents and overcome partial obstruction of the pylorus caused by postoperative adhesions. Closure of the perforation, gastro-enterostomy, and pyloric

exclusion should be the method of choice in the treatment of perforated pyloric and duodenal ulcers. Simple closure of the perforation should be reserved for only those patients whose general condition is so poor that even a rapidly performed gastro-enterostomy would be too much of an operative risk.

The Bacteriology of Infected Wounds with Especial Reference to the Importance of Streptococcus Hemolyticus.—SWEETSER (*Annals of Surgery*, 1921, lxxiii, i, 4), gives the data and conclusions based on an analysis of a bacteriological work done at Base Hospital 15 of the A. E. F. Anaërobes are prominent in the early bacteriologic picture of wounds but disappear in a short time. Aërobes become progressively more prominent. The streptococcus has a fairly constant incidence and is very persistent. A combination of Streptococcus hemolyticus and Staphylococcus aureus was the most common of all associations in wounds. That association was particularly frequent in fatal wounds. Streptococcus hemolyticus, Staphylococcus aureus, Bacillus welchii, Bacillus coli communis, Bacillus proteus, and to a less extent, Staphylococcus albus, were the bacteria appearing most often in both the fatal and non-fatal cases. The prognosis seems to have been good in cases showing Staphylococcus aureus or other aërobes aside from streptococcus. Here the most interesting point is that an association with Staphylococcus aureus seemed to lower the virulence of infection with anaërobes. Infections with anaërobes showed a high death-rate, but a short-period of danger to life, unless the anaërobes were associated with streptococcus. Deaths from streptococcus infection were numerous and occurred at least up to the end of the fourth month. The mortality was even higher where streptococcus was associated with Staphylococcus aureus or with anaërobes. Conversely: Cases fatal early usually showed anaërobic infection; those dying late invariably showed streptococcus infection. Most of the early improvements and cures were cases of infection by aërobes other than streptococcus, while the improvements and cures that were tardiest generally showed infection by streptococcus without anaërobes, or by streptococcus and Staphylococcus aureus without anaërobes. Secondary suture of wounds failed in some cases apparently because the interval between the injury and primary surgical treatment had been too long, and in other cases because the secondary suture was attempted too soon. Gas infection was most often found in wounds of heavily muscled parts of the body; fracture of bone was not an essential factor; anaërobes frequently contaminated without infecting wounds. A streptococcus bacteremia was apparently by far the most important cause of death in cases of gunshot wound. The culture of infected wounds is certainly valuable, even if only for the purpose of determining the presence of Streptococcus hemolyticus.

Reduction of Old Dislocations of the Hip by Open Incision.—BUCHANAN (*Surg., Gynec. and Obst.*, 1920 xxxi, v, 462) says the exact time at which an unreduced dislocation of the hip becomes old cannot be definitely stated, but traumatic hip dislocations may be considered old at the end of four weeks. Reduction by manipulation is rarely successful after that time, owing to formation of connective tissue,

which fills the acetabulum and binds down the head and neck. Reduction by open incision is to be preferred in nearly all cases of old hip luxations and with modern methods is attended with but little danger. Preliminary traction by Buck's extension is of advantage. The actual replacement of the head, after the acetabulum has been emptied and the head and neck released, is best accomplished by manipulation or the use of levers with manual and body traction. The result is often ideal and, in the cases reported, has been good in 80 per cent.

PEDIATRICS

UNDER THE CHARGE OF

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Report of a Case of Malignant Thyoma with Necropsy.—Foot (*Am. Jour. Dis. Children*, July, 1920) reports a case of a boy aged nine years who died during anesthesia for an exploratory operation. On necropsy a very hard, lobulated mediastinal tumor was found, occupying chiefly the anterior mediastinum. It lay just behind the sternum, but did not infiltrate the bone. Metastases by direct lymphatic extension were seen with three possible minor metastases at a distance. The lungs and neighboring organs were not penetrated much more deeply than their serous coverings. The tumor was composed chiefly of small cells resembling microlymphocytes, but having vesicular nuclei, acidophile cytoplasm and tending very slightly to anastomose with one another by means of slender processes. This was seen only in a very few, most being collagenous connective tissue. Neighboring lymph glands showed a few discrete cells in their sinuses, but were not, as a rule, incorporated in the tumor mass. A review of the literature of this subject, together with information from this case, seems to point rather strongly to an epithelial origin of the tumor. At first the cells seem almost identical with the microlymphocyte, but once it begins to differentiate the similarity rapidly is lost. While it would seem wisest not to emphasize too strongly an argument based on a series of transitional changes pieced together from a group of cases occurring in individuals of different ages and reported by a number of observers, such a series is very suggestive and not unsupported by supplementary evidence from the embryologic standpoint. There are small celled sarcomatoid tumors as well as carcinomatous. In the tumor studied here there was little reason to consider it as of infectious origin, while there was a great deal to point toward its being a true neoplasm. There seems little doubt that these small-celled thymic tumors, whether lymphosarcomas or not, are still of thymic origin, and are different from the lymphosarcomas that arise in lymph nodes.

Infrequency of Intestinal Parasites in Young Children.—McLEAN (*Jour. Am. Med. Assn.*, June 26, 1920) made a study to determine the

frequency of helminthiasis in children attending the out-patient department in New York City. A number of studies have been made in recent years to determine this point, but most have been done on children over three years of age and in institutions where the incidence of disease is higher than in children living at home. The out-patient department where the stools were examined is not a neighborhood clinic, but the patients come from all parts of the city, and are perhaps of a class superior in intelligence and receiving better hygienic care than the attendants at a neighborhood clinic. The studies covered a period of five months and were made at random without any reference to symptomatology. Many of the examinations were made on stools from children who came to the clinic along with a sick brother or sister. Others came only for vaccination. It was found that a history of symptoms commonly associated in the minds of the laity with the presence of intestinal parasites could be elicited frequently from the parent of children over twelve months of age. These were restlessness at night, grinding of teeth, picking the nose and lips, loss of weight, capricious appetite and irritability. Examinations were made on 208 stools in children up to twelve years of age, 2.27 per cent. harboring parasites. There were 3.7 per cent. of positive examinations in 189 examination of children from two to twelve years. In a group of 69 children from four to twelve years, 5.7 per cent. were positive. In 53 stools of infants in the first year and 66 in the second year no parasites or ova were found. If the statements of the parents could be accepted regarding their findings of worms in the stools the percentage would be higher. Fruit skins and strings of mucus may be readily mistaken for worms by the anxious parent, and this accounts for the number of cases in which the parasites have been seen by the mother and not found in the laboratory.

Fat Metabolism in Health and Disease.—HUTCHINSON (*Quart. Jour. Med.*, April, 1920) found from a study of the stools that the digestion of fats in infantile atrophy, rickets and tetany is carried out as efficiently as in healthy children. The fat output in the feces varies directly with the fecal weight and formed approximately one-third of this. In order to determine whether the percentage absorption was normal or not it was necessary to take the fecal weight into consideration. When the fat intake was under 20 gm. per day both fat intake and fecal weight affected the percentage absorption; the fecal weight was the predominating factor. When the intake was over 20 gm. per day the intake was not considered and the percentage absorption depended on the fecal weight. The lower average percentage absorption in infantile atrophy was due to the lower average fat intake. There was a slightly greater loss of fat in infantile atrophy due to the stools being larger than in healthy children. The excessive loss can be neglected as far as nutrition is concerned as there is not a true deficient absorption. In rickets the excess loss of fat per day over that in healthy children average 0.6 gm., which is a sufficient amount to affect nutrition. In tetany the loss was 2.4 gm. per day, which was due chiefly to the passage of larger stools and to a less degree to a true deficient absorption. Since the fat in the feces averaged 38 per cent. other facts point to a normal fat absorption in infantile atrophy, such

as the increased amount of fat absorption, with an increased intake and the fact that improvement frequently follows lowering of the fat content of milk. Saponification of fats in the intestine does not affect the absorption of fats. The author points out that the fairly constant percentage of fat in the feces of man and other animals suggests that fecal fat has a function, although he does not suggest what the function may be.

OBSTETRICS

UNDER THE CHARGE OF

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Seven Hundred and Fifty Obstetric Cases in Private Practice.—REEVES (*Jour. Kansas Med. Soc.*, 1919, p. 177) gives the results of his experience with private patients in his obstetric work. Thirty-two per cent. of these were primipara. His statistics showed the usual frequency of presentations while his percentage of bladder operations is not excessively high, 11.2 per cent. As was to be expected, out of 88 operations 58 were done in primipara. In 3 per cent. of his patients he performed version, 23 cases, and this was done for three indications: (1) posterior rotation of the occiput; (2) transverse position with shoulder presentation; (3) eclampsia. The writer believes that version done at the proper time is a more safe and easy operation than the use of high forceps. No Cesarean sections were done in this series, although in the writer's opinion it would have been better to have done this operation in three cases. In two of these version was done and in the remaining case the forceps was used. The mothers survived, but the children were lost. The writer had five patients with eclampsia, two of whom died. All of the children survived. Two hours after delivery by forceps a primipara, aged twenty-nine years, had inversion of the uterus. There were 5 cases of mammary abscess in primipara after they had left the writer's care. Three patients had puerperal sepsis, one of whom was infected by the dirty hands of a drunken husband, the case terminating fatally. The second patient was infected by unclean dressings and infection developed in the third case after version for an impacted breech presentation. There were 2 cases of fibroids complicating labor, one of which was delivered of a macerated child by forceps and hysterectomy was subsequently done; while in the other the fibroid caused a severe postpartum hemorrhage because the uterus could not contract. There were 2 cases of premature separation of the placenta, in both of which the child was lost. A young primipara died soon after delivery and another two hours after an easy forceps delivery, without hemorrhage. Autopsy failed to reveal an adequate cause for death. There were 4 cases of postpartum bleeding: 1 from uterine inertia following the birth of twins in a primipara, 1 from uterine fibroids, 1 where a placenta was adherent and retained and 1 where a uterus failed to contract in a primipara after

she had been delivered by forceps. Twins were seen in 11 cases, triplets once. Only 0.5 per cent. of the mothers of the writer's patients could not nurse their children. The writer used pituitrin in 78 cases, in 2 of which there developed hour-glass contraction of the uterus, with retained placenta. His experience leads him to believe that the safest dose of pituitrin is 5 to 7 minims, and that all larger doses are distinctly dangerous.

Glycosuria in Pregnancy.—CAMERON (*Canadian Med. Assn. Jour.*, 1919, p. 723) in examining the urine of a patient in the fifth month of pregnancy found small quantities of a reducing sugar.

The Prolonged Retention of the Placenta.—LENCANE and PROMSY (*Ann. de gynec. d'obst.*, October, 1919) contribute a paper concerning the possible relationship of growths of the chorion and retained fragments of placenta. Fragments of placenta are often retained in the uterine cavity for a considerable time. They are sometimes considered benign tumors, capable of assuming malignant characteristics. The writers believe that a change from placental tissue to chorionic epithelium is altogether exceptional, and so far has not been proved. A placental polyp should not be considered a benign tumor for it does not grow by the proliferation of its own elements which extend into adjacent tissue as tumors usually do. The best conception of the retained placenta is that it is a sort of graft which may continue to survive occasionally for a long time through the maternal circulation, which in the end is either absorbed or eliminated. The accumulation and organization of clotted blood produces the apparent increase in the size of this region, portions of the placenta, and this is comparable to a thrombosis which grows along the bloodvessel. These prolonged retentions of placental tissue are residue with a precarious life, having only a transient existence in the organ where they are retained.

Inversion of the Uterus and the Report of a Case of Sixteen Months' Standing.—BOYD (*Am. Jour. Obst.*, 1919, lxxx, 161) reports the case of a woman in her third labor, delivered by forceps of a child weighing nine pounds. There was free bleeding after delivery, and when the uterus was compressed suddenly the fundus left the operator's hand and the uterus and vagina became completely inverted. A firmly adherent placenta was attached to the top of the uterus. The hemorrhage was alarming and continued until the placenta was detached. An attempt was immediately made to replace the uterus, but failed, and seven hours after delivery the patient was anesthetized and a second attempt made to invert the uterus by taxis. This was unsuccessful. Abdominal section was performed and the constricted cervix was dilated by inserting the fingers through an abdominal incision into the crater-like cavity. At the same time pressure was made on the fundus through the vagina and the uterus was replaced. A douche was given and the uterus firmly packed with gauze. Complete recovery in the third week of the puerperal period ensued. A second case was that of a primipara who had a prolonged but spontaneous labor. The placenta was adherent and traction was made and inversion of the uterus occurred. The patient stated that she bled freely and that a mass protruded out of the vulva.

The physician who attended the patient did not recognize the nature of the difficulty and made no attempt to replace the uterus, but told her that this tumor should be removed in forty days. During the puerperal period there was free bleeding, but no other complication, nor did symptoms of infection develop. The mother nursed her child until it died at the age of eleven months. Seven months later she had free bleeding, for which she was obliged to remain in bed. Her physician then told her that the uterus was out of place. About a year and a half after the original accident the true state of the case was discovered. At that time involution had taken place, but the uterus was completely inverted, filling the cavity of the vagina, and when touched bled freely. After the parts had been made as aseptic as possible a metal catheter was introduced into the bladder, the perineum was depressed and the uterus was drawn down with a double tenaculum inserted in the fundus. A transverse anterior vaginal incision was made just above the cervix and the bladder separated without opening the cul-de-sac. A median longitudinal incision was then carried through the anterior lip of the cervix, thus removing the cervical constriction. An attempt was made to replace the uterus, but without success. The anterior cul-de-sac was opened and a longitudinal incision made in the anterior wall of the uterus to completely sever the uterus and this was carried to within 1 cm. of the fundus. When the cavity of the uterus was laid open the tubes were found invaginated, but normal and without evidence of adhesions. The uterus was replaced by pulling upon the divided lips of the cervix and forcing the fundus upward with the thumbs. This produced a bulging of the anterior uterine wall, which required partial resection in order to close the uterus accurately. The tissues were brought together by catgut sutures and the vagina replaced in the pelvic cavity. The vaginal incision was closed after the peritoneum had been sutured to the uterus. A gauze drain was placed in the vaginal wound between the bladder and the uterus and another in the uterine cavity. Aside from the mild infection, with slight fever, the patient made a good recovery.

A Modification of Porro's Operation.—LECOQC (*Ann. de gynec. d'obst.*, October, 1919) describes an operation done in 1911 by his former chief, Reymond. He had occasion to remove a pregnant uterus at term containing a living infant without the preliminary opening of the womb, treating it as one would a large fibroid tumor. In this way loss of blood was prevented, mother and child making a good recovery. Lecocq himself has done this in 4 cases, losing one mother from peritonitis, but saving all the children. The indications for this procedure are those recognized for hysterectomy or Porro's operation. They are probable infections of the uterus in cases in which birth through the natural passages is impossible or highly dangerous. Again, when the uterus contains fibroids or malignant growth and rapid delivery must be done because uterine rupture is threatened, when there is complete uterine inertia and Cesarean section is indicated and when the patient has placenta previa with severe hemorrhage, or has hemorrhage into the uterine muscle, and also to obviate the danger of osteomalacia. In doing the operation one proceeds as in hysterectomy, clamping the broad and round ligaments, incising the peritoneum anteriorly and

stripping off the bladder. The uterine arteries can then be made out and clamped and the vagina or cervix is cut across rapidly. When the second uterine artery is clamped the circulation of the mother in the pelvic regions is threatened, and this may bring about asphyxia in the child. To obviate this the writer advises that one of the uterine arteries be cut between two clamps and that the vagina or cervix be severed near the second artery, so that when everything is ready the second artery is clamped and the uterus removed. The assistant to whom the uterus is given opens it on the anterior wall, removes the child, ties its cord and if necessary resuscitates. The operator finishes the operation then as in an ordinary hysterectomy.

Cesarean Section.—ESSEN MÖLLER (*Arch. mens. v. oster o. et de Gynec.*, April, 1919) gives the results in 106 cases of Cesarean section at the Maternity at Lund and raises the question as to whether obstetricians should save the child in this way at considerable risk to the mother. He believes that the results are now so good that the operation should be done when any reasonable indication exists. In 10 cases done for eclampsia 3 died, but the operator had waited until the patients were in desperate condition before operating. He thinks vaginal Cesarean section preferable in eclampsia when the condition of the tissues permits. For placenta previa seven sections were done, one woman dying, probably from embolism. Fatal embolism after even version has been known in these cases. He would not have recourse to Cesarean section after placenta previa unless hemorrhage was profuse, the cervix not sufficiently dilated for versions and the mother certainly not infected. In one patient Cesarean section was done, although it was known that the child was dead. Hemorrhage during the operation was very little, much less than if one had waited for a spontaneous dilatation of the cervix. In operating for myomatous tumors complicating pregnancy he first abstracts the child and then removes the uterus. He considers abdominal Cesarean section much better than version or embryotomy. The woman is free from infection. When, however, the slightest suspicion of infection arises he tries version or forceps to avoid perforation of the living child. If the conditions are such that the child cannot be born living, or if there are absolute indications for it, Porro's operation is performed. In 8 cases of this sort all of the mothers recovered. The most important point is to decide when the operation should be done. The writer does not have faith in prophylactic measures nor does he believe in waiting until the woman is in danger of infection. He believes that in discussing Cesarean section the result obtained for the children should be regarded as well as for the woman. Only one child was lost, and this occurred from umbilical hemorrhage, which might have been avoided. The other 105 infants were safely born except the seven that were stillborn and one that succumbed to the effect of malformations.

Estimation of Fats, Cholesterol and Sugar in the Blood of Thirty Pregnant Women.—SCHILLER (*Surg., Gynec. and Obst.*, November, 1919) examined the blood of 14 pregnant women in the later months of gestation, 10 who were at term, 5 who had been delivered and one in the third month of pregnancy. The object of his research was to estimate the

fats, cholesterol and sugar in the blood. In making this investigation he reviewed the work of Morris, Letschke, Kemperer, Simmons, Hermann and Neumann. In studying the presence of cholesterol he injected a watery extract of corpus luteum into the blood, which produced rapidly a temporary hypercholesteremia. A similar result was obtained from adrenalin. Evidently there is a close relation between the endocrine glands in pregnancy and the increase in fats and lipoids. The conclusion of his experiments led him to believe that in the later months of pregnancy after the first two weeks in the puerperal period there is no hyperglycemia. During this time glycosuria and alimentary glycosuria are explained by the activity of the glands of internal secretion or as a hyperrenal function. In pregnancy hyperlipemia is for the most part a hyperlipoidemia. There seems to be no distinct parallelism between cholesteremia and hyperglycemia in pregnancy. While we must believe that the endocrine glands are an important factor in this matter, the etiology of the condition has not yet become established.

OPHTHALMOLOGY

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Intra-orbital Foreign Bodies and Orbitotomy.—MERCIER (*Paris Thesis*, 1920) has made a study of intra-orbital foreign bodies, the material for which has been increased greatly by the war. An intra-orbital foreign body, if it is voluminous is easily recognized, for it betrays its presence by immediate symptoms of reaction to which is soon added an assemblage of very variable signs depending upon the damage occasioned by the projectile within the orbit (exophthalmos, paralysis of ocular muscles, pupillary disturbances, lesions of the optic nerve, or of the deeper membranes of the eye). If, however, the foreign body be but small, it frequently remains unperceived; under these circumstances radioscopy and radiography, according to the technic recommended by Velter, are indispensable, both for determining the presence and seat of the projectile. As soon as a positive diagnosis has been made, and it is of the greatest importance that this be done as soon as possible after the accident, the foreign body should be extracted, whatever its size, for tolerance is never definite, and sooner or later, serious accidents will supervene, which it is manifest should be avoided. Early intervention also facilitates cleansing of the wound and path of the projectile and permits of primary sutures. As it is indispensable to locate precisely the seat of the projectile by radiography before operation, radio-

scopic control is frequently very useful but unfortunately practicable only in a small number of hospitals. The operative procedure recommended by Mercier consists of orbitotomy with curvilinear incision of the orbital margin, while avoiding injury to the tissue of the conjunctival and palpebral apertures, and detachment of the periosteum from its external origin to the bottom of the orbit. The eyeball is then pushed aside and the region methodically explored with the palmar surface of the finger turned toward the globe. As soon as the projectile is felt, it is to be laid bare with a cannulated sound and extracted by forceps; the orbitotomy is done under local anesthesia; it is preferable to Krönlein's operation of bony resection. The site of the incision depends upon the seat of the foreign body; it may be external, infero-external, inferior, infero-internal; internal, supero-internal, superior, supero-external. The above operation suffices in the majority of cases; it permits not only extraction in case the foreign body has penetrated beyond the limits of the orbital cavity; but it also facilitates cleansing of the wound, removal of clots and contused tissue, as well as chips of bone. The lips of the wound should be sutured immediately after intervention, with occasional drainage for two or three days. The results are normal as a rule; shock is reduced to a minimum and the chances of infection are reduced to a minimum.

Lessons Gathered from the Observation of 12,000 Cases of Trachoma During the War.—STAIKOVICI and LOBEL (*Archiv d'ophtal.*, November, 1920, p. 34), as the result of treatment of 12,000 cases of trachoma, come to the following conclusions: Notwithstanding the favorable results from surgical intervention, the treatment of granular conjunctivitis should aim at cure with the least possible destruction of the palpebral conjunctiva. The treatment should be individualized for every case. Frictions with medicaments, particularly sulphate of copper, practiced for a considerable time and especially in recent cases, appear to give the best results. It is indispensable to recognize the disease in the earliest phases of its evolution and to begin intervention at the earliest possible moment. As regards corneal complications, intervention must be begun early, either by peritomy in cases of pannus, or by subconjunctival injections when ulceration is present, without, however, intermitting the usual treatment. The lacrimal passages should also be kept under observation and the proper treatment instituted when necessary. In entropion and trichiasis, extirpation of the tarsus with preservation of the conjunctiva by careful dissection, is the procedure of choice.

Ocular Tension as an Autonomous Contractile Function of the Choroid.—NICATI (*Archiv d'ophtal.*, August, 1920, p. 449) concludes that the eye possesses an autonomous contractile function, the purpose of which is to maintain a constant equilibrium between the ocular tension and the arterial tension of the retina, which he terms the reflex *contre-cœur*. This function is seated in the choroid, a musculo-vascular contractile sac, with its own innervation, Müller's ganglion. Ocular tension depends upon the degree of repletion of the choroidal vessels; it is, besides, dependent upon global contraction of the choroid, as shown by transitory augmentation from excitation of the cervical

sympathetic. Accidental spasmodic contraction of the choroid, ocular colic, during the operation for cataract, causes, according to its intensity, presentation or loss of vitreous and hemorrhage, and when the latter is very intense, hernia of the choroid (expulsive hemorrhage). Ocular colic may also be reflex as when the aqueous humor is evacuated suddenly by puncture of the cornea. The painful attacks of spasmodic glaucoma are of a colicky nature; they are caused by excitation of Müller's ganglion from pressure. Acute, subacute and chronic primary glaucoma with hypertension is the consequence of paralysis of the choroid due to lesions of Müller's ganglion, the paralysis entraining choroidal stasis and edema which the flow of aqueous humor is unable to compensate. Secondary glaucoma is due to retention of the aqueous humor, the latter being no longer able to find an exit through the crypts of the atrophic or obstructed iris. Hypotension occurs in iritis, where it is the expression of participation of the choroid in the inflammatory process in certain cases of detachment of the retina and as the terminal stage of glaucoma.

Hot Springs in Ocular Affections.—NETTO (*La Clin. Ophtal.*, October, 1920, p. 544) observes that in diseases of the eyes, the water of hot springs may be employed either by means of their vapors, local or general baths, or internal use, but their use is contraindicated in acute states. Lesions of the anterior segment are most suitable for thermal treatment. Lesions of the fundus require special care in the application of immersion baths; the temperature of the latter should be 35° C.; they are contraindicated in severe cases. Thermal baths aggravate affections of the optic nerve and deeper membranes. In ocular affections requiring sudorific treatment, thermal baths which provoke abundant perspiration are not to be recommended; in these cases general light radiation is to be preferred; the latter is also indicated in diseases of the fundus, stimulating the sudoriparous glands from which result slight perspiration and evaporation and thus inhibit accumulation of heat in the organism. The various forms of iritis, particularly the gonococcic are markedly improved by immersion baths. As lavage, the thermal springs frequently exert a favorable influence upon the various forms of conjunctivitis attended by abundant secretion. The radio-active waters have an undoubted influence upon inflammation of the conjunctiva, including trachoma.

Spectacles in Japan.—ONISHI (*Klin. Monatsbl. f. Augenhk.*, July, 1920, p. 123) observes that there is no doubt but that spectacles were first brought to East Asia from Europe partly by sea through Singapore by Portuguese or East Indians, partly by land through Samarcand (1387 A.D. to 1432 A.D.) At this period, these articles were great rarities and very dear: in the age of Mins, a single pair of spectacles was valued at the price of a horse. Whether spectacles had made their appearance in these regions earlier than the above date, is difficult to determine; the writer considers it probable that the well known Franciscan monk Giovanni, the pioneer missionary to China, may have brought a pair to Peking in 1293, spectacles having been discovered in Italy shortly before this date, and the missionary was of the age when optical aid was needed for near work. Spectacles were brought thence to Japan,

probably by F. X. Xavier; the latter made many valuable presents to the ruler of Yamaguchi, among which was probably a pair of spectacles. At this period, foreign merchants, Chinese or Portuguese, introduced spectacles into commerce in Hiroshima. The art of grinding spectacles is said to have been acquired by a certain Hamada in 1630 from the Dutch of Batavia or Formosa, while the Chinese brought the art about the same time to Nagasaki. The art of making glass was introduced about the year 800 into China from Rome or Constantinople by way of Turkestan, with which country China already at that early date carried on active commercial relations. The glassmaking art appears to have been known at a very early age in Japan, as the ancient term "Tamazukuribe," crystal maker, testifies; but it seems gradually to have been lost. Renewed fabrication of glass appears to have been again introduced as late as 1624-1643 into Nagasaki by Portuguese and Chinese.

Vossius's Lenticular Ring.—BEHMANN (*Klin. Monatsbl. f. Augenhk.*, February, March, 1920, p. 255) reporting three cases of Vossius's lenticular ring, concludes that the opacity is due to the impression of the pupillary margin upon the anterior surface of the lens; the mechanism of the impression is brought about by the action of the contusing force in such wise as to depress the cornea, so that cornea, iris and lens are brought into momentary contact: through transudation of a sero-fibrinous substance, the pigment adheres to the anterior surface of the lens giving rise to the ring or disk. In typical cases, the pigment deposit is left without any damage whatever to the capsule or cortical layers: that the opacity consists of pigment and not of blood or folding of the capsule, is proved by the demonstration of particles of pigment in the aqueous humor and upon the posterior surface of the cornea: these consist of the same material as the individual particles of the ring; while in the case of hemorrhage, upon disappearance of the blood, the opacity in the anterior chamber vanishes also, whereas the particles of pigment remain visible for a number of days. The opacity as a rule is occasioned by a force which acts upon the globe directly from in front; an identical opacity can also occur from an action upon the posterior section of the globe. Clearing of the opacity progresses from the center outward; the duration of the phenomenon averages about fourteen days; when more protracted, lens lesions must be assumed which are not a part, however, of a typical ring.

Xeroderma Pigmentosum.—CHEVALLEREAU and OFFRET (*Annal. d'oculist.*, April, 1920, p. 236) report a case of xeroderma pigmentosum in a boy of thirteen with good family history. The affection began two years before the report with a small papule at the canthus of the left eye; at the same time several other small papules appeared upon the face. As regards the disease of the left eye, the physician who first saw the lad, reports a tumor of the limbus involving the cornea and conjunctiva, strongly adherent, rose colored, readily bleeding and the size of a small hazel nut; the tumor was removed but recurred at once and increased enormously. Microscopic examination showed it to be an epithelioma of extreme gravity. The eye was enucleated by extensive incision of conjunctiva and healthy tissue: healing normal. The follow-

ing lesions are now present: face; classic manifestations of xeroderma pigmentosum; here and there small telangiectasies and atrophic white spots. The dominating lesions are yellow pigmented spots, some slightly raised, forming small tumors particularly upon the lower lids. Near the commissures of the lips and upon the alæ of the nose, are small, dry, warty horns, some ulcerated and infected; lymphatics not enlarged. The hollow of the right ear is filled with a tumor springing from the border of the antitragus; this tumor is mamelonated, sanious and covered in large part by a brownish membrane. The right eye presents a tumor upon the inner part of the sclero-corneal limbus, slightly involving the cornea—a papillary epithelioma. This growth, as well as those of the face and ear, were removed; they were all found to consist of Malpighian pavement epithelium in various stages of malignancy, from the precancerous of the eye to evident malignancy of those of the skin and especially the ear. All the sections showed inflammatory lesions intimately connected with neoplastic formations; numerous cocci, for the most part of the diplo variety, were noted. As regards therapeutics, the history of xeroderma pigmentosum teaches that this disease requires an extremely sombre prognosis; DuCastel writes that it is exceptional for the patient to live long beyond adolescence. In this case the roentgen rays were energetically applied with manifest amelioration; although in Darier's opinion radiotherapy should not be employed in Malpighian epitheliomas.

Errors of Diagnosis in Ophthalmology.—VOGT (*Cor.-Bl. f. Schw. Aerzte*, No. 4, vol. xlix) gives the following brief summary of diagnostic methods for recognizing important ocular conditions which may easily be overlooked. Foreign bodies: Before operating, make careful examination with the roentgen rays; also sideroscopic test. Very fine deposits in torpid cyclitis: Loup and mirror, Hartnack's loup; corneal microscope. In unilateral glaucoma, careful search for deposits to distinguish between secondary and primary affection. In doubtful cases, test tension only with tonometer of Schiøetz: many pseudo-glaucomas can be recognized by this instrument; prolonged determinations of the tension should be made without a miotic; if the tension is found to be normal under these circumstances, cautiously instil a mydriatic and repeat the tonometric tests. Difficulty of seeing the lens in exudations into the pupil where Purkinje's images, the slit-lamp and sunlight are negative: in cases of this kind the method by fluorescence will frequently succeed. Differential diagnosis between optic neuritis and edema of the papilla, frequently so difficult, is facilitated by Gullstrand's ophthalmoscope; with this instrument prominences of the papilla, very circumscribed in the beginning come out clearly. It is interesting to note that in edema, the tissue of the papilla remains transparent for a long time. In inflammation adaptation to obscurity remains below normal for a considerable period, unlike in edema; in the former, also, narrowing of the visual field in sectors or other forms occurs sooner than in the latter. Green (red-free) light may also be utilized, for ordinarily in neuritis the retina is involved from the beginning, as may be recognized, particularly in youthful subjects, by the appearance of preretinal lines of reflection with double contours, an appearance often clearly apparent with the green but invisible to

ordinary light. In recent retrobulbar neuritis, lines of this nature, as well as the texture of the nerve fibers come out more clearly, while the macular reflex is modified or disappears entirely: in this condition, all other objective signs are absent. With green light, acute or subacute retrobulbar neuritis, frequent prodrome of sclerosis *en plaques*, will not go unperceived: the wrong diagnosis of hysteria will thus be avoided.

Autoplastic Restoration of Eyebrows.—MORAX (*Ann. d'ocul.*, May, 1920, p. 286) makes the interesting remark that the arch of the eyebrows, unlike the common belief that it has no other role than an esthetic one, possesses a very useful function in that it prevents the entrance of the perspiration from the brow into the eye. In the case of a palpebro-frontal burn, the absence of such a dam came out very unpleasantly and, in fact, it was this which caused the patient to consult Morax. Autoplastic restoration may be accomplished by two different autoplastic methods: autoplasty by displacement of pediculated, hair bearing, cutaneous flaps taken from the maxillary region of the opposite side (in case of unilateral alopecia of the eyebrow) or from the temporo-frontal region. This method is extremely satisfactory in complete alopecia of both eyebrows; by its means, hairbearing grafts can be obtained to any desired extent and of perfect symmetry. It is the method of choice whenever possible, that is where the temporo-frontal region has not been denuded of hair by cicatricial alopecia. Autoplasty with non-pediculated hair-bearing flaps may also give good results, but they are uncertain, and when successful, the number of hair follicles which survive transplantation are always greatly reduced as compared with the follicles originally present in the grafted tissue. This procedure, the techic of which is undoubtedly capable of improvement, may be applied where the neighboring hair-bearing regions (temporofrontal, bearded cheek) have been deprived of their hair follicles or are not adapted to autoplasty with a pediculated flap.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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A Study of the Relation of Family Income and Other Economic Factors to Pellagra Incidence in Seven Cotton-mill Villages of South Carolina in 1916.—GOLDBERGER, WHEELER and SYDENSTRICKER (*Public Health Reports*, November 12, 1920, No. 46, xxxv, 2673) present the results of a careful study of the subject, in which the various factors are fully considered. In this discussion it is pointed

out that the receipt of an adequate income does not necessarily guarantee an adequate diet, as individual tastes may have a predominating influence. It is suggested that economic depression may lead to an increased pellagra incidence in 1921. The following quotation of part of the discussion and of the summary and conclusions is presented: The very great importance of food availability in relation to pellagra prevalence seems heretofore not to have been very clearly recognized. Under some circumstances, as we have shown, this factor may operate notably to affect the character of the diet and thus the incidence of the disease. Our data dealt with differences in availability between localities of relatively small area, but it is readily conceivable that analogous differences may exist between areas of great extent such as there is reason to believe actually is the case between the northern and southern parts of the United States. This difference is probably an important factor (together with the well-known difference in dietary habit, Sydenstricker, 1915) in the notable inequality in the incidence of the disease in these two sections of the country. The results of the present study clearly suggest fundamental lines along which efforts looking to the eradication of the disease should be directed, namely, (1) economic, by improvement of economic status (income), and (2) food availability, by improvement in availability of food supplies. Measures for improving the economic status of those people most subject to the disease, are in the main, outside of the sanitarian's sphere and but little subject to his influence. While much the same may be said to apply to the conditions of food availability, this field is more easily accessible, both directly and indirectly, to his activities and influence. Thus, for instance, by avoiding ill-considered regulations governing milk production he can, negatively at least, favor an adequate supply of this invaluable food. Furthermore, he can and should aid in improving the conditions of food availability by lending his powerful influence in support of and, by coöperating with, the agencies at work in this field, in their efforts to stimulate milk production (particularly through cow ownership) and to induce the farmer to adopt a suitable system of crop diversification. And in this connection it may perhaps be remarked that certain preliminary observations have created in our minds a rather strong suspicion that the single-crop system as practiced in at least some parts of our southern states, by reason of apparently unfavorable conditions of food supply and of other conditions of an economic character bound up therein, will be found indirectly responsible for much of the pellagra morbidity and mortality with which local agricultural labor is annually afflicted. Although considerable study will be required to determine definitely the factors responsible for the high incidence of the disease in the rural areas in question, it would, nevertheless, seem to be the part of wisdom to make an earnest effort to improve conditions in the ways suggested above. The authors draw the following summary and conclusions: (1) In the present paper are reported the results of the part of the pellagra study of cotton-mill villages, during 1916, dealing with the relation of conditions of an economic nature to the incidence of pellagra. It is the first reported study in which the degree of the long-recognized association between poverty and pellagra incidence is measured in a definite,

purely objective manner. (2) The study was made among the white mill operatives' households in seven typical cotton-mill villages of South Carolina. Pellagra incidence was determined by a systematic, biweekly, house-to-house canvass and search for cases, only active cases being considered. Information relating to household food supply, family income, etc., was secured by enumerators for a sample section of the period April 16 to June 15, assumed to be representative of the season during which the factors favoring the production of pellagra were assumed to be most effective. (3) Family income was made the basis of classification according to economic status, the Atwater scale for food requirements being used for computing the size of families in comparing their incomes. (4) In general, pellagra incidence was found to vary inversely according to family income. As the income fell, the incidence of the disease rose and showed an increasing tendency to affect members of the same family; as the income fell, incidence fell, being reduced almost to the point of practical disappearance in the highest of our income classes, although the income enjoyed by this class was comparatively quite low. (5) The inverse correlation between pellagra incidence and family income depended on the unfavorable effect of low income on the character of the diet; but family income was not the sole factor determining the character of the household diet. (6) Differences in incidence among households of the same income class are attributable to the operation of such factors as tend to determine the amount and proportion of family income available for the purchase of food, the intelligence and ability of the housewife in utilizing the available family income, and to the differences among households with respect to availability of food supplies from such sources as home-owned cows, poultry, gardens, etc. (7) Differences in incidence among villages whose constituent households are economically similar, are attributable to differences among them in availability of food supplies resulting from differences (a) in the character of the local markets, (b) in the produce from adjacent farm territory, and (c) in marketing conditions. (8) The most potent factors influencing pellagra incidence in the villages studied were (a) low family income, and (b) unfavorable conditions regarding the availability of food supplies, suggesting that under the conditions obtaining in some of these villages in the spring of 1916 many families were without sufficient income to enable them to procure an adequate diet, and that improvement in food availability (particularly of milk and fresh meat) is urgently needed in such localities.

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ORIGINAL ARTICLES.

THE BREATHING OF AIR OF LOWERED OXYGEN TENSION
AS A TEST OF CIRCULATORY FUNCTION.

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Henderson and his co-workers^{2 3} have recently reported favorably on the value of gradual lowering of oxygen tension of respired air by means of a rebreathing apparatus as a test of cardiac function. While these workers speak of the test as one of cardiac function, it is apparent that the work of the heart alone, in the adaptation to anoxemia cannot be separated from that of the circulatory function as a whole.

The response to anoxemia involves a number of body mechanisms, the relative importance of which has not been definitely settled. Gregg, Lutz and Schneider⁴ state that individuals differ in their responses to low oxygen tension, pointing out that some compensate

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² Jour. Am. Med. Assn., 1918, lxxi, 1382. Schneider, E. C.: Jour. Am. Med. Assn., 1918, lxxi, 1384. Whitney, J. L.: Jour. Am. Med. Assn., 1918, lxxii, 1389.

³ Air Service Medical, Washington, D. C., 1919.

⁴ Am. Jour. Physiol., 1919, I, 216.

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largely by increased respiration, while others depend almost wholly on increased blood-flow. Haldane, Kellas and Kennaway,⁵ on the other hand, hold that anoxemia cannot be compensated for by mere increase in breathing or circulation; the advantage gained by higher saturation of the blood with oxygen in the lungs is counteracted by the increased sweeping out of carbon dioxide which results in shifting of the dissociation curve for oxyhemoglobin. Owing to this, the hemoglobin combines more readily with oxygen in the lungs but holds on to it more tightly in the tissues, so that the supply is not much improved, although the blood is redder.

We have attempted to determine the usefulness of tests with the rebreathing apparatus for clinical purposes in hospital work, especially with respect to its value in estimating circulatory efficiency. We have made a number of studies on presumably normal individuals, also convalescent hospital patients who had no anemia, lung disease nor apparent circulatory deficiency, as well as a few patients with pneumokoniosis and a number with varying degrees of circulatory inadequacy. A great many of the tests were not satisfactory, as it is difficult to get patients from hospital wards and out-patient departments to coöperate perfectly in a procedure that gives them some inconvenience and sometimes unpleasant sensations. We have selected for presentation at this time, studies on a few cases with advanced disease; two with pneumokoniosis and five with either narrow margins of cardiac reserve or actual broken compensation. In all the hemoglobin percentage was 75 or more (Sahli). None showed any arrhythmia nor developed any during the test except occasional slight sinus arrhythmia coincident with increased breathing. The cases of pneumokoniosis were fairly well advanced in the so-called second stage. They were studied in the effort to learn to what extent pulmonary lesions of their type might be expected to interfere with the aëration of the blood while breathing air with lowered oxygen content.

Methods. A rebreathing apparatus was used similar to the one described by Henderson.¹ The volume of air used was an amount on which the subject, if he were normal, might be expected to reach the limit of this tolerance in about thirty minutes. Respiration rate, blood-pressure and pulse readings were taken for several minutes after the mask was adjusted, but before the actual test was begun. Notes were made on the clinical findings at this time. After the patient began breathing into the apparatus, blood-pressure readings and pulse-rate observations were noted every minute; frequent examinations of the heart were made and the general condition and the color noted.

Although the observers in the Air Service⁵ have found psychological tests of extreme importance in the study of the reactions of

⁵ Jour. Physiol., 1919, liii, 181.

aviators, the tests described by them were scarcely practicable in individuals of the grade of intelligence found in hospital wards, many of whom are foreigners. We were compelled to resort to simple tests, such as affirmative or negative signs to questions. By this method we have avoided carrying any of our subjects to complete unconsciousness, but still have been able to test them close to the limit of psychic efficiency, where it manifested itself before physical distress.

Where feasible, exercise tests have been carried out with a Martin type of bicycle ergometer. Cardiac cases were usually tested with 6000 foot pounds of work in two minutes. Observations were made as with respect to any apparent distress or exhaustion, pulse reactions and dyspnea. Air breathed during the exercise and the next minute was collected in a Douglas bag and the quantity expired measured by an experimental gas meter. When the ergometer tests could not be carried out, observations were made on reactions to simple exercises such as stair-climbing.

SUMMARY OF CASES.

CASE I.—I. W., white, male, aged forty-five years; coal miner. Diagnosis. Osteo-arthritis of lumbar spine; second stage pneumokoniosis. The diagnosis of pneumokoniosis was made by x-ray. No evidence of cardiovascular disease. Only symptoms were those referable to the osteo-arthritis. Good response to lowered oxygen tension (Chart I).

CASE II.—T. H., white, male, aged forty-nine years; potter. Diagnosis. Pneumokoniosis, second stage; pulmonary emphysema; general vascular sclerosis; chronic constipation. Has been a potter for over thirty years and has had "potter's asthma" for many years. Becomes short of breath on exertion. X-ray showed second stage pneumokoniosis. Exercise tolerance fair. Performed work of 6000 foot pounds easily but with more than the usual hyperpnea. Good response to lowered oxygen tension (Chart II).

CASE III.—J. N. H., white, male, aged twenty-seven years; laborer.

Diagnosis. Valvular heart disease (aortic stenosis and regurgitation, mitral regurgitation). History of rheumatic fever and repeated attacks of tonsillitis. Shortness of breath on climbing stairs or ladder. Palpitation especially at night interfering with sleep. Examination showed slight cyanosis of lips, ears and finger tips; very large heart with transverse measurement of 18 cm. and the signs of advanced disease of the aortic valve, and also mitral involvement. The response to 6000 foot pounds of exercise in two minutes on the bicycle ergometer was poor. He became exhausted, there

was hyperpnea and marked pulse reaction. Fairly good response to lowered oxygen tension (Chart III).

CASE IV.—A. O., white, male, aged thirty-two years; blacksmith's helper.

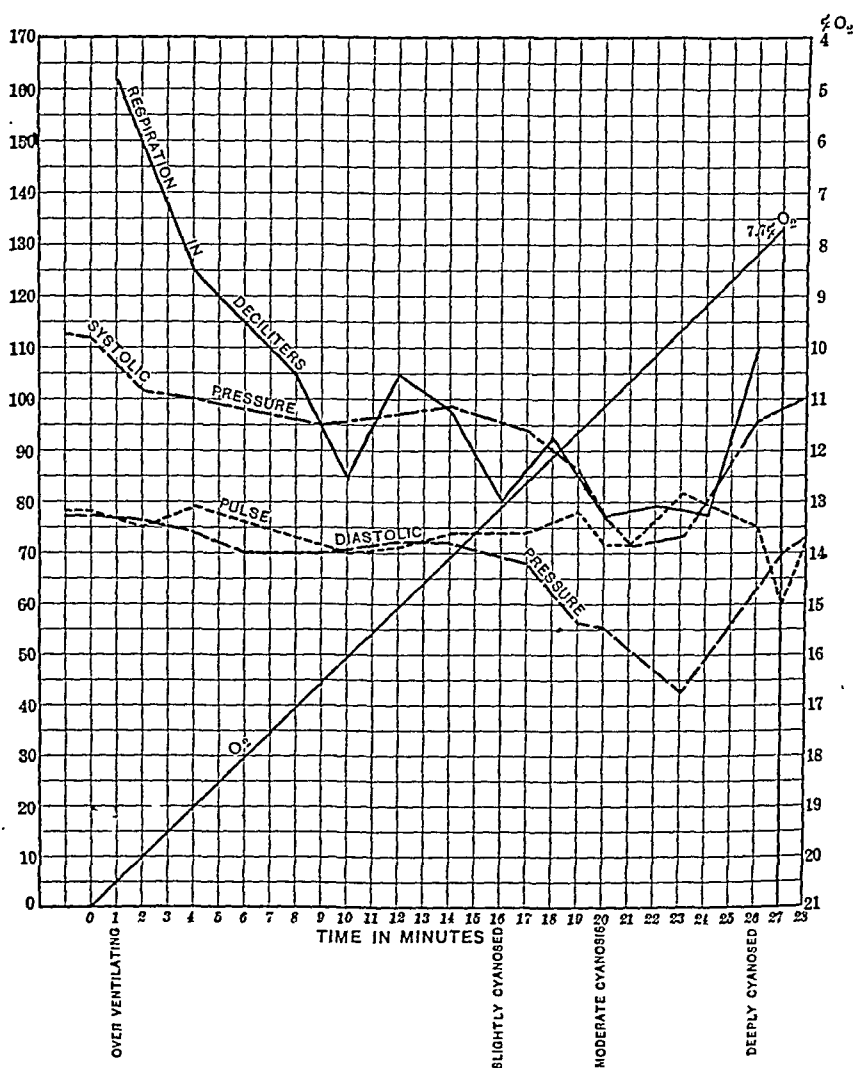


CHART I

Diagnosis. Valvular heart disease (mitral regurgitation); slight decompensation. History of rheumatic fever twelve years ago. Shortness of breath on exertion and palpitation; much worse recently. Cough for five weeks. Examination showed slight

cyanosis of lips, ears and finger tips, slight edema of ankles. Transverse measurement of cardiac area 17.5 cm. Moist rales at bases of both lungs. After ten days' rest, cyanosis, rales and edema disappeared. The rebreathing test done at this time showed fairly good response to lowered oxygen tension (Chart IV).

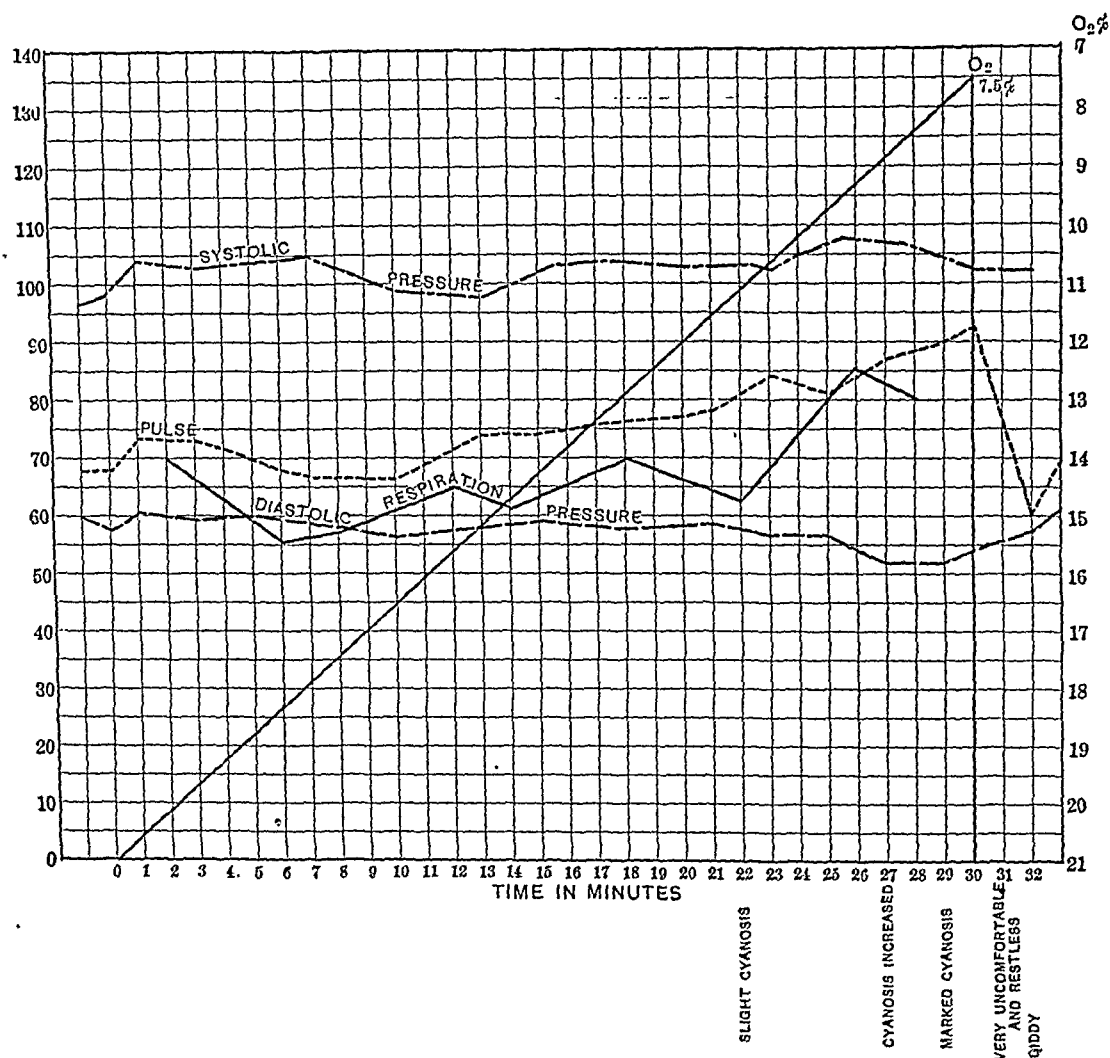


CHART II

CASE V.—J. O. N., white, male, aged forty-nine years; motorman.

Diagnosis. Valvular heart disease (mitral stenosis); slight decompensation. Rheumatic fever twenty years ago. Recently, shortness of breath and palpitation on slight exertion; cough worse at night with occasional blood-tinged expectoration, and swelling of feet and legs if he stood much. Examination showed slight orthopnea, transverse cardiac measurement of 16.5 cm., presystolic thrill and murmur. Lungs were somewhat emphysematous, with many moist rales at both bases. The reaction to exercise was poor.

He was barely able to do 6000 foot pounds in two minutes on the ergometer. The dyspnea was quite marked but the pulse reaction was not excessive. The response in the rebreathing test was fairly good (Chart V).

CASE VI.—M. W., white, female, aged twenty-eight years; housewife.

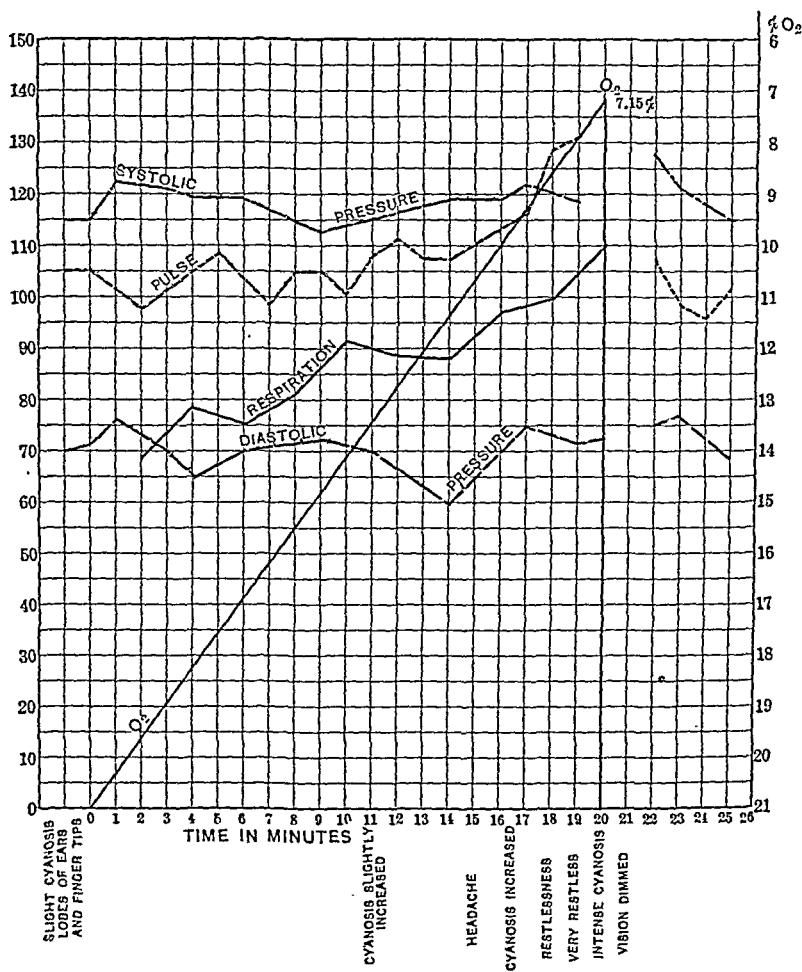


CHART III

Diagnosis. Valvular heart disease (mitral stenosis). History of attacks of rheumatic fever, nine and seven years ago. For the past three years acute attacks of weakness, shortness of breath and palpitation after exertion; recently had a very severe attack that kept her in bed several days. Examination showed the heart enlarged, with a transverse measurement of 14 cm. Presystolic thrill and murmur, accentuated pulmonic second sound. Few moist rales at

bases of both lungs. Pulse-rate unstable, usually normal in the morning, but frequently 100 to 115 in the afternoon. Tolerance to exercise very poor. Dyspnea and marked tachycardia, also a complaint of palpitation on climbing a flight of stairs. The response to lowered oxygen tension was poor (Chart VI).

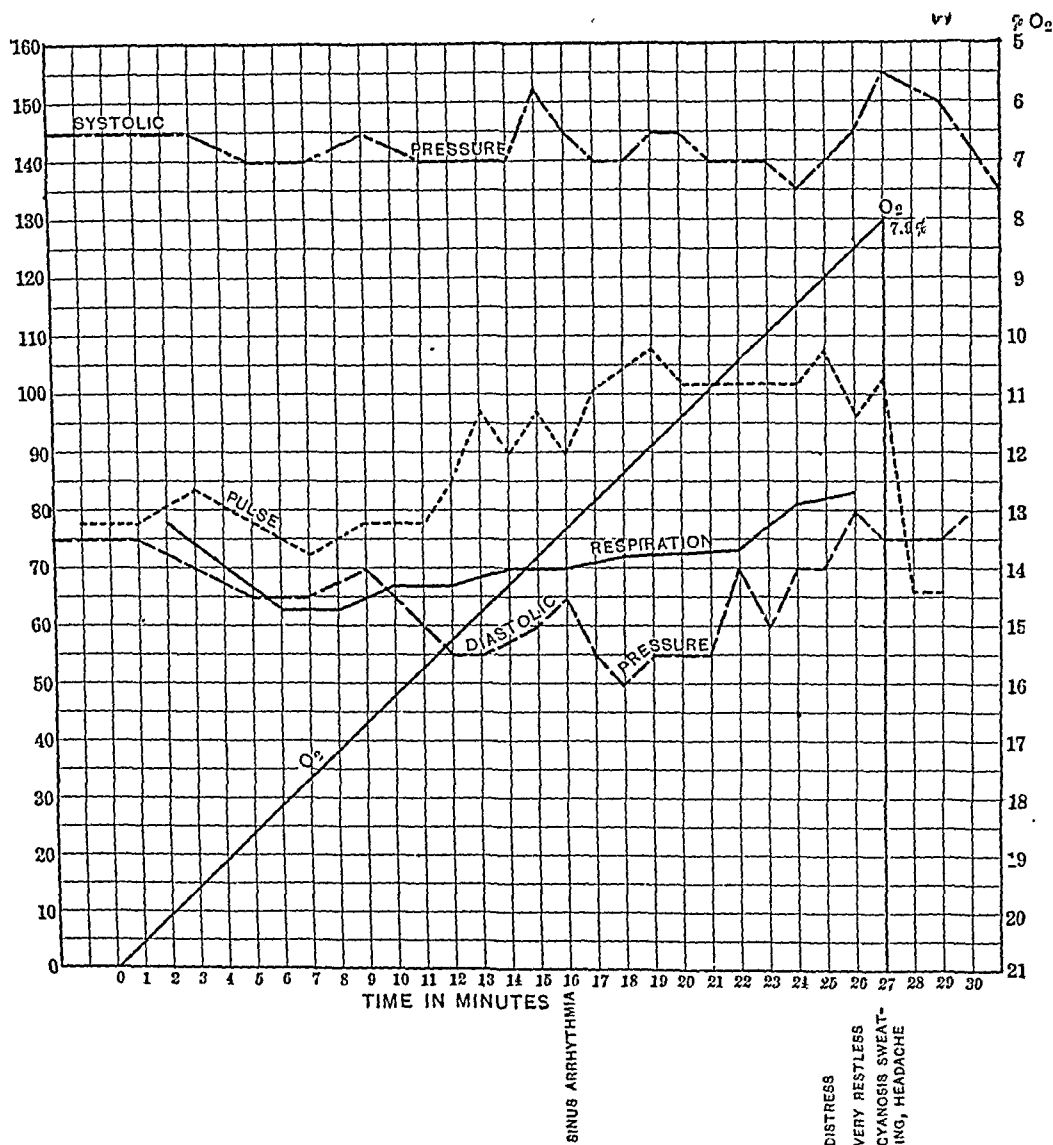


CHART IV

CASE VII.—F. M. B., white, male, aged twenty-seven years; printer.

Diagnosis. Valvular heart disease (mitral stenosis); cardiac decompensation. History of scarlet fever and repeated attacks of tonsillitis. Shortness of breath for three years, but three months ago it became so severe that he was unable to walk. Also had

palpitation and vertigo. Improved somewhat recently. Examination showed slight cyanosis of ears and finger tips. Heart enlarged; transverse measurement 16 cm. Presystolic thrill and murmur at apex. Many moist rales at the bases of both lungs. Liver extended three finger-breadths below the costal margin in the midclavicular line. Urine contained a cloud of albumin and

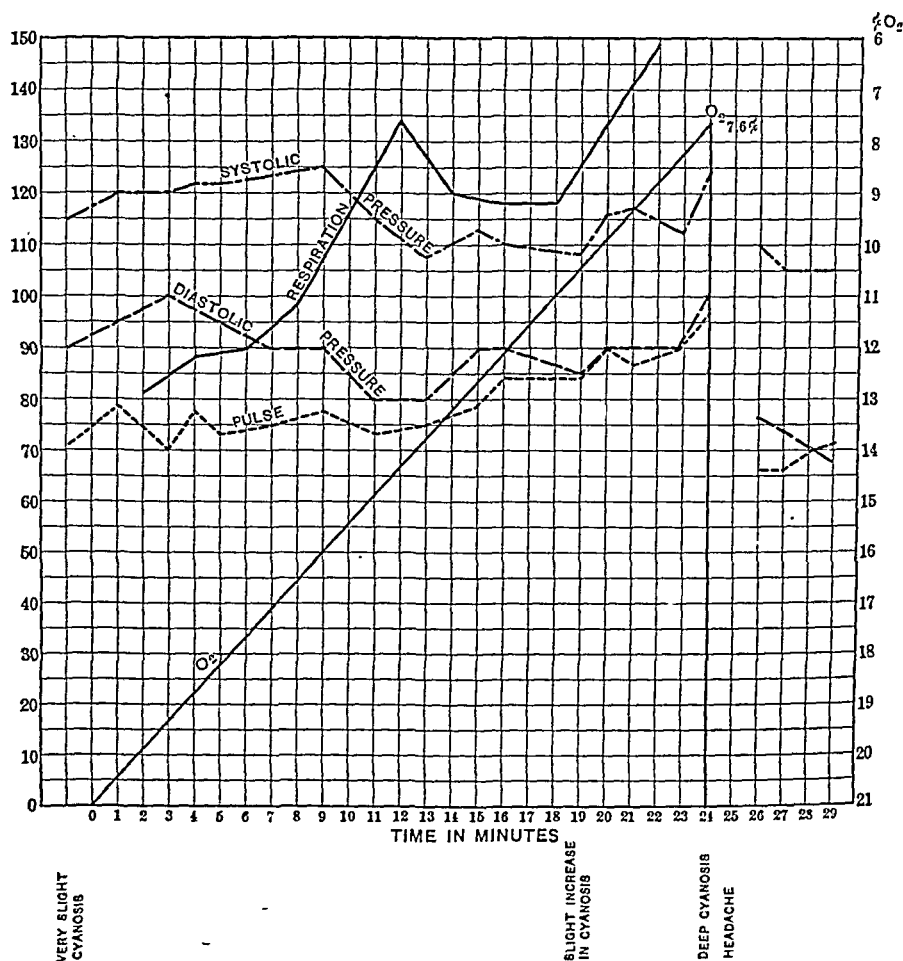


CHART V

many casts. Phthalein elimination 37 per cent. in two hours. The reaction to lowered tension of oxygen was poor (Chart VII).

Comment. In view of the comparatively slight respiratory increase that usually occurs in anoxemia, it was to be expected that moderately advanced pneumokoniosis would not interfere very materially with the ability of an individual to compensate for

low oxygen. This proved to be the case in two examples of this condition.

Some of the results in cardiac cases were unexpected. If the heart always played an important part in the compensation for anoxemia in all the cases presented, we should have expected an early breakdown in the rebreathing test. Early failure did indeed occur in two of the five cases—notably in the one with the most

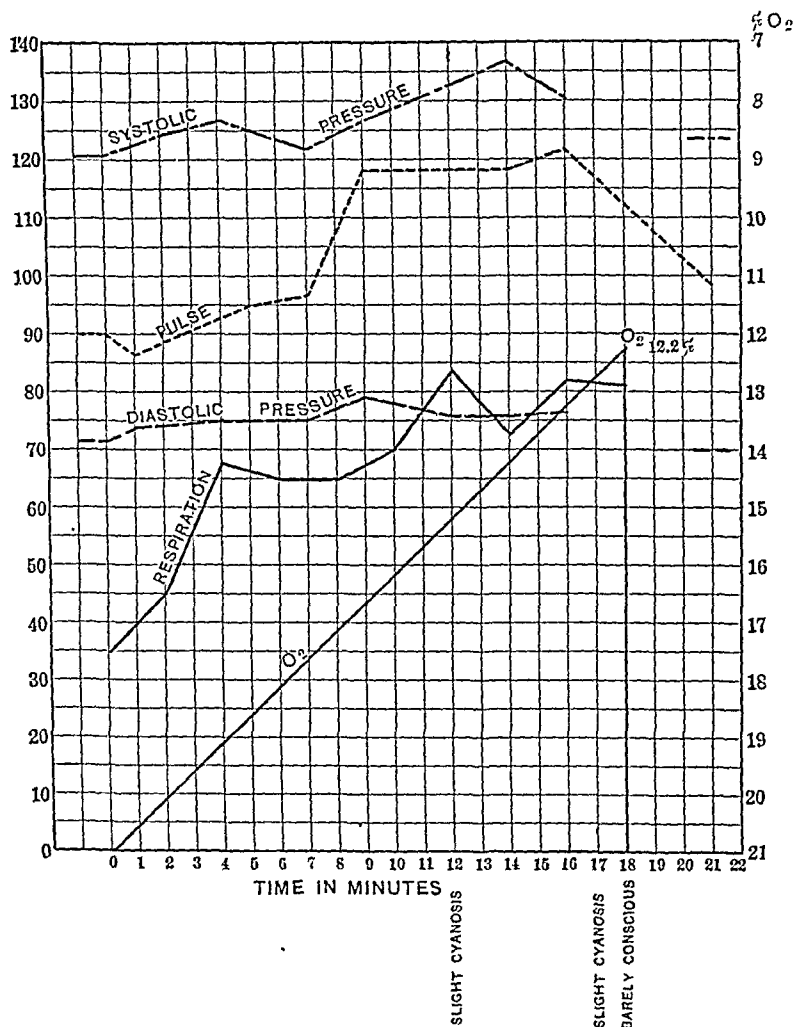


CHART VI

advanced decompensation (Case VII). In these two cases, apparently, demands were made on the circulation that could not be met. In the other three cases however, and notably in two with clinical evidences of broken compensation (Cases IV and V) in which the reserve power of the heart must have been seriously limited, the comparatively good runs in the rebreathing test must have been made possible by efficient compensation through extracardiac mechanisms.

While the rebreathing test may offer a good indicator of the general fitness of an individual, the part the heart plays in any case in the adaptation to anoxemia is particularly difficult to evaluate because there occurs a coördinating of several mechanisms, some of which are known, doubtless others unknown. We have failed to

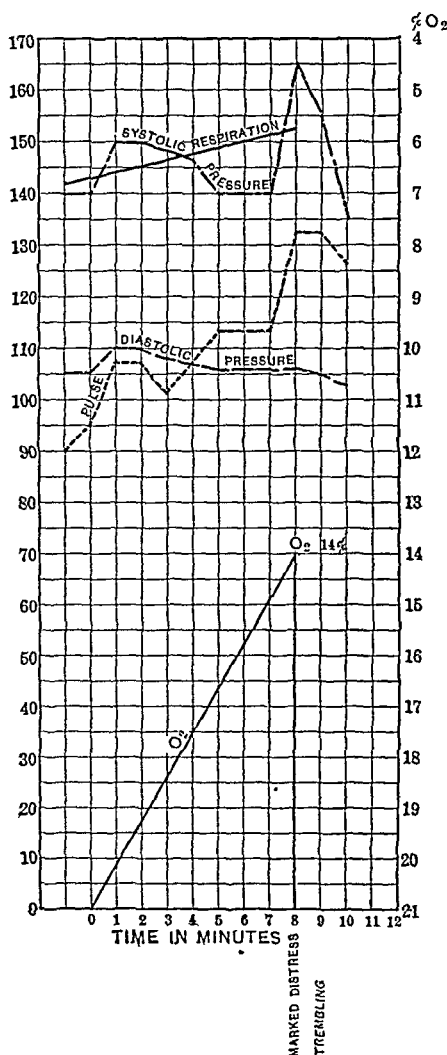


CHART VII

discover more than a moderate demand for increased cardiac function, in cases that we have tested, having been unable to demonstrate appreciable enlargement of the heart, either by observations on the position of the apex impulse, or by percussion of the area of cardiac dulness; nor have we observed the marked

engorgement of the vessels of the neck that almost invariably accompanies acute dilatation of the right side of the heart.

The variations in response to the anoxemia produced by means of the rebreathing apparatus, among cases with, at most, narrow margins of cardiac reserve, appear to justify the conclusion that the test does not furnish a trustworthy index of cardiac function.

BRONCHO-ESOPHAGEAL FISTULA AND TRACTION DIVERTICULUM.

BY JOHN B. HAWES, 2D, M.D.,

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THE name "broncho-esophageal fistula" is self-explanatory, although the condition itself may be classified as one of the rarer lung complications. "Traction diverticulum" of the esophagus, differing only slightly in etiology and course from a simple broncho-esophageal fistula, is a still rarer complication, and one that finds scant mention in the literature. In the eighth edition of Osler's *Practice of Medicine* it is described as follows: "Traction diverticulum, situated in the anterior wall near the bifurcation of the trachea, results, as a rule, from extension of inflammation from lymph glands, with adhesion and subsequent cicatricial contraction by which the wall of the esophagus is drawn out. Diagnosis of this condition is now readily made with bismuth meal and roentgen ray." Osler mentions one case of an esophago-pleuro-cutaneous fistula in the right infraclavicular region which communicated with a cavity in the upper part of the pleura or lung. Osler and McCrae¹ describe a traction diverticulum as one caused by pressure from without; often it causes no symptoms. Tuberculosis of bronchial lymph nodes is a frequent cause. Little mention of either traction-diverticulum or broncho-esophageal fistula is to be found elsewhere in text-books on clinical medicine, while in works on pathology it is referred to briefly and as a rarity.

The diagnosis, as in one of my cases, is sometimes made by recognizing in the sputum particles of food eaten some time previously. Dr. W. H. Smith, of Boston, told me that he discovered one case purely by accident when on passing a stomach tube he met with an obstruction, and on withdrawing it found in the end of the tube several drops of pus which on examination was found to contain tubercle bacilli. The diagnosis of tuberculosis of the lungs and mediastinal glands was then confirmed by roentgen ray. Usually the diagnosis is impossible without a fluoroscopic examination. Dr. George W. Holmes, roentgenologist to the Massachusetts

¹ Modern Medicine, iii, 94.

General Hospital, has described to me an experience of his in regard to this: A patient suspected of having malignant disease of the gastro-intestinal tract was given the usual barium meal, the passage of which down the esophagus Dr. Holmes observed with the fluoroscope. To his surprise and considerably to his alarm, he saw a portion of the barium instead of going down into the stomach side-switched off into what were apparently cavities resulting from a cancerous involvement of glands around the lung root. The patient, however, suffered no unpleasant consequences in any way from thus having barium introduced into his lungs. It was his experience in this case in which the barium in the lung apparently did no harm that led me to risk this procedure in one of the cases herein described. One of these seen in consultation with Dr. Wyman Whittemore, and here presented with his kind permission, is an example of a simple broncho-esophageal fistula following an acute pulmonary infection, with resulting abscess of the lung; the other one of my own is a true traction diverticulum of the esophagus of some years' duration.

CASE I.—G. T., aged thirty-seven years, a shoe-factory worker by trade, entered the west medical service of the Massachusetts General Hospital, November, 1919. One brother had died of tuberculosis. He gave a history of "pleurisy" at the age of eight years. His maximum weight was 148 pounds one year previous; his present weight was 130 pounds. Seven months ago he first noticed clubbing of his finger nails. His present illness began eleven months ago, when he was taken acutely sick with fever, pain in the right back and much cough and sputum. His physician told him that he had pneumonia. Five weeks after this a roentgen-ray examination was made which showed a consolidation of the right lung. A diagnosis of lung abscess was then made. Chest tap was negative. Soon after this he began to cough up as much as one pint daily of thick yellow sputum. Occasionally there was some clear blood. At the time of his admission he had constant pain in the right lower back, with considerable cough and sputum.

Physical examination showed dulness, with bronchial breathing, increased fremitus, crackling rales over the right upper one-third of the chest, with flatness, diminished voice and breath sounds and bronchophony at the right base behind. The heart was normal. He raised 20 to 24 ounces of sputum daily, which consisted of foul, bloody pus without tubercle bacilli. Wassermann test was negative. Roentgen ray showed a pathologic process within the right lung, with involvement of the pleura, appearing as "a dull, rounded area in the right lower chest." January 24, 1920, he was transferred to the surgical ward and operated on by Dr. Whittemore, who resected a rib and drained the abscess. February 1, 1920, it was first noticed that fluids which the patient drank partly came out through the

drainage tube in the wound in the back. This was conclusively demonstrated by giving him a drink of water containing methylene blue, which could be seen coming out through the tube. A bismuth roentgen ray was taken which showed clearly a sinus from the esophagus leading into the lungs. The report of this examination was as follows:

"February 12, 1920. Fluoroscope. A moderate portion of the barium mixture passed freely through the esophagus; a smaller portion was seen traversing the right lung field in an irregularly branching channel to the periphery of the chest. It appeared to leave the esophagus at a point opposite the upper portion of the aortic arch, but this area was not clearly seen on account of what appeared to be a superimposed density in the lung shadow.



FIG. 1.—Arrow points to mass of glands at hilus of lung, probably the site of the traction diverticulum.

"The plate shows extensive dulness in the lower one-half of the right chest, as previously described. This dulness now rises to the level of the third interspace and is of a somewhat irregular density. Through this dulness can be faintly seen shadows of a small quantity of barium described in the fluoroscopic note. Diagnosis: Broncho-esophageal fistula."

The discharge from the opening in the back gradually lessened, the fistula healed up and the patient was discharged from the hospital April 5, 1920, apparently well.

Here then is a case of simple broncho-esophageal fistula following an acute pulmonary infection. The fistula healed spontaneously and the lung seemed to suffer no ill effects from the passage through it of barium or food, liquid or solid.

CASE II.—This patient was referred to me by Dr. W. H. Kenny, of Winchendon, Mass. S. H., a married woman, aged forty-two years, with two healthy children, aged seven and ten years respectively, first came to see me July 18, 1919. Her father died at seventy her mother at sixty-five years. She has three brothers and four sisters alive and well, but had lost one brother and one sister of tuberculosis. She stated that she had always been considered delicate, but except for frequent attacks of bronchitis had had no serious illness. Her maximum weight was 147 pounds at the present time. For the past fifteen or sixteen years she has had a slight hacking cough, with scanty sputum but no other symptoms. She stood childbirth splendidly, and her lungs were always declared to be sound.

In January, 1916, she came down with influenza while at the same time her children had whooping-cough. In her desire to look after them she got up too soon, had a relapse and for the first time had a copious pulmonary hemorrhage amounting to a "bowlful of blood." She was in bed three months, with marked weakness and loss of weight from 132 to 113 pounds. For a long period she had daily hemorrhages and was very seriously sick. In May, 1916, she gave up her home in Boston, where she was then residing, and went to live in the country, having been told definitely that she had consumption. Since August, 1917, although she has gained steadily in weight and strength, about once a month, practically always associated with her menstrual periods, she has had hemorrhages varying in amount from one or two teaspoonfuls to two or three ounces of clear blood. In the winter of 1917-18 she went to Florida and had three slight hemorrhages while there. At the time of this examination she had a good appetite, ate and slept well, and was without pain, fever or other symptoms except moderate shortness of breath. She was naturally in a very nervous condition on account of so frequent bleedings.

Physical examination when I first saw her in July, 1919, was practically negative except for the lungs. Here there was fairly definite evidence of an old, apparently tuberculous process in the right middle and upper lobes, with dulness in the region of the spine of the scapula, increased whispered voice and breath sounds and numerous dry rales. Roentgen-ray examination was as follows: "There is a well-rounded diaphragm of moderate excursion, not limited by adhesions. The heart shadow seems normal. There is considerable diffuse thickening at both lung roots in the peribronchial structures, with some old, calcified glands. There is moderate peribronchial infiltration about the finer bronchioles, particularly toward the right apex, and there is an area just in from the tip of the right scapula at the lung root in which the peribronchial structures are particularly thickened. There is some emphysema about this area and there is apparently what would seem to be a small cavity

here and also a thickened pleura between this upper and middle lobe of the lung. Aside from the calcified glands in the left lung root, with the very moderate peribronchial thickening upward, there is no evidence of any lesion on the left. We believe the hemorrhage could well come from this spot at the right lung root, which we believe to be probably tuberculous and fairly well localized."

As was to be expected I made a definite diagnosis of chronic, moderately advanced, pulmonary tuberculosis, despite the fact that my examinations and former examinations of the sputum had been negative.

December 4, 1919, I saw her again in consultation with Dr. Kenny at her home. She had done very well until five weeks ago, when



FIG. 2.—Lateral view of chest. Upper arrow points to esophagus partially filled with barium. Lower arrow points to shelf-like sinus on which part of the barium could be seen leaving the esophagus on its way to the lung.

she again started to raise blood in small amounts. About one week before this she had a slight attack of laryngitis, with a marked increase in the amount of sputum up to 6 or 7 ounces. This when I saw her had gradually decreased to normal. At this time her lungs were in apparently the same condition as before. The sputum consisted of pure pus full of pneumococci, but contained no tubercle bacilli, while her general condition was much improved. At this visit both the patient and her husband referred to the curious fact, which they were at a loss to explain, that particles of food eaten several hours previously were coughed up in the sputum. She was certain that these particles were coughed up and not vomited. She also noticed on swallowing an occasional sense of constriction or pressure to the left of the sternum near the fourth or fifth rib.

Dr. Kenny, her family physician, confirmed all these statements and wrote me as follows:

"For a number of years she has observed at times, twenty-four hours and more, after eating certain foods, such as oranges, that after coughing the sputum would contain particles of the above-mentioned food. She also has "coughed up" tablets or pills twelve hours after she had swallowed them, with merely the outside coating gone. I observed this morning particles of food mixed with purulent sputum, although she had taken no nourishment for three hours. You remember the pain she spoke of just to the left of the median line which would follow the act of swallowing food. Now I am wondering if it may be possible that she has a diverticulum of her esophagus and that it in some manner pressed on a bronchus and has caused ulceration of the same, finally breaking through it."

In January, 1920, this patient came to the Massachusetts General Hospital for further study. Here another roentgen ray was taken and likewise a fluoroscopic examination made while the patient was swallowing a barium mixture. Concerning this, Dr. George Holmes, roentgenologist to the hospital, reports as follows: "Fluoroscopic observation showed fairly good respiratory movements of the diaphragm on both sides; the costophrenic angles are clear. To the right of the spine, in the region of the lung root, there is a distinct area of increased density, in the center of which there are bright spots suggesting cavity formation. This process is somewhat nearer the back than the front of the chest and extends outward nearly to the mid-portion of lung. In the lateral view no mediastinal masses could be made out.

"Patient then swallowed some barium mixture. The bulk of this passed readily through the esophagus into the stomach, but there was a portion which seemed to rest in a shelf-like process in the esophagus opposite the lung root and near the point in which the area of increased density was noted in the lung. When the patient had taken a slightly greater amount of barium mixture it was seen to pass from this shelf into the bright areas previously noted, which had the appearance of cavities.

"A series of plates, including anteroposterior and lateral views, before and after taking the barium mixture, confirm the fluoroscopic observation, and show in the area described at the lung root a small, dense, round spot in the extreme outer portion of the invaded area. This spot is slightly further out in the lung field and rather more dense than the average calcified gland, and the possibility of its being a foreign body should be considered. The bright areas described in the fluoroscopic observation are even more noticeable in the plates and are probably due to cavity formation. The lung markings throughout both lungs are considerably thickened, but the thickening is most evident around the larger bronchi and in the lower parts of the chest. Such a thickening could be entirely due

to repeated infections. The apices and periphery of the lungs are clear. I can see no positive evidence of tuberculosis in the parenchyma of the lung. The process at the right lung root is probably chronic inflammatory. It may be or may not be of tuberculous origin. The examination with the barium mixture demonstrates a sinus communicating between the process in the lung and the esophagus."

Dr. Holmes and I both considered very carefully the question as to whether or not, in view of the fistula doubtless existing between the esophagus and the lung, the swallowing of barium could do any harm. We both felt confident, however, that if particles of food—orange, cascara tablets, etc.—that had been known to go down via the esophagus and came up by way of the trachea did no harm that a simple barium mixture would likely prove innocuous. That we were justified in this opinion has been shown by the subsequent course of events. Although previous to this time hemorrhages even under a most careful regimen were fairly frequent since leaving the hospital in January, 1920, when she was first given the barium meal, up to the present (June 1, 1920), she has had only one small hemorrhage, while her general condition has improved steadily.²

This case has been interesting in the extreme and the results so far at least very satisfactory to all concerned. Here was a woman in whom a definite diagnosis of pulmonary tuberculosis had been made by her family physician in 1916 and by myself in July, 1919, based on (1) signs in the lungs and (2) hemorrhages. Her husband gave up a flourishing law practice and went with his wife to live in the country. The patient, a very conscientious woman, had practically isolated herself from her children for fear of infecting them. As a result of careful study from my point of view it has been fairly well established:

1. Although the original infection of the mediastinal glands may have been one of tuberculosis this is not necessarily so nor definitely proved.

2. The patient is in no way a source of danger to those about her in view of repeated negative sputum examinations and her own high degree of intelligence.

3. It is no longer absolutely necessary for her to live an isolated life in the country, but, on the other hand, perfectly safe for her to reside within easy reach of Boston, where she and her husband's interests are located.

4. Finally although she has had and doubtless will have further hemorrhages, they will probably do her little or no harm, it having been shown that the process in her lungs is not a progressive one.

² Her general condition still remains good, but at intervals she still has severe hemorrhages, November, 1920.

From the physician's viewpoint this case has been an instructive one. It has more than ever confirmed me in my belief that the physician, who makes a definite diagnosis of pulmonary tuberculosis in the absence of a positive sputum, takes upon himself a grave responsibility. He should look at the case from every angle, from the patient's as well as from his own point of view, and should weigh carefully every bit of evidence pro and con before telling the patient that he is a consumptive.

It has likewise taught me that although the majority of pulmonary hemorrhages are due to tuberculosis, there are many of non-tuberculous origin, and that there are still more, that, although undoubtedly of a tuberculous nature, do not indicate active tuberculosis or that that patient needs anything more radical in the line of treatment than careful supervision and applied common sense.

Finally, I have been impressed with the fact that foreign bodies in the lung, in this instance, particles of food, cascara pills and barium do not have the disastrous effects usually supposed to be the case but that they may pass through the lung, as in Case I (broncho-esophageal fistula), to an opening on the outside, or pass from the esophagus to a cavity connected with the mediastinal glands and from here into the bronchi and out through the trachea, as in Case II (traction diverticulum), without apparently causing any disturbance or doing any harm.

CHRONIC NEPHRITIS: FROM THE POINT OF VIEW OF THE GENERAL PRACTITIONER. ITS DIAGNOSIS, PROGNOSIS AND TREATMENT.¹

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WHEN one examines the shelves of any complete medical library or merely goes over the titles on the subject of nephritis in any of the medical indexes and sees what an enormous number of volumes, monographs and articles were published on the subject in the last five to ten years, one must realize that in the time allotted to me we cannot possibly hope to adequately cover the ground. I have therefore decided to discuss the subject from the point of view as it affects the general practitioner and to raise only those problems which confront us daily in the management of these types of cases.

¹ Read before the Harlem Medical Society, October 13, 1920.

The Classification of Chronic Nephritis. Pathologists have taught us that we have a number of different types of chronic nephritis, namely:

1. Chronic parenchymatous nephritis with large white kidneys.
2. Chronic diffuse nephritis.
3. Chronic interstitial nephritis with small, contracted kidneys.
4. Amyloid kidneys, fatty kidneys, etc.

It is exceedingly interesting to note these differences in the anatomic structure of the diseased kidney as it appears on the autopsy table. But up to the present the most careful work, examination of blood, urine and kidney functional test have not yet enabled us to tell definitely whether in the living patient we deal with one type of kidney involvement or another. What we do know definitely is that we have a disturbance in the kidney function and that the different patients group themselves (1) according to the character of the physiologic disturbance and (2) according to the severity of the disturbance.

Besides, it is an open question today whether the anatomic differences that we observe on the autopsy table really represent different diseases which run their characteristic courses or whether they are different stages of progress in one and the same disease. The subject has recently been admirably discussed by Eli Moschowitz. He brings evidence in favor of the latter view, and I feel convinced that the time is not far distant when that will be the accepted view of all clinicians and pathologists.

When I say that a patient has a phthalein output of 35 per cent. with a limited capacity for water and salt excretion while his nitrogen excretion is normal; or when I say that another patient has a capacity for normal phthalein output, excretes water and chlorides perfectly, but falls behind in his nitrogen excretion and shows retention of nitrogenous substances in the blood, we have given a decidedly clearer way of classifying our nephritic patients than if I said that the patient suffers from chronic diffuse nephritis or chronic interstitial nephritis. In the former way we can express the severity of the affection in definite mathematic figures and the progression or retrogression of the case can be followed, whereas by the latter classification we are left entirely in the dark. We therefore, from the practical point of view, must abandon the anatomic classification and take up the classification of our cases according to their disturbed physiologic function.

The Causes of Chronic Nephritis. It is in the nature of human inquisitiveness to look for a cause for every disturbance in the normal run of events. It is also natural for us to find something to blame it on. In regard to chronic nephritis, if we find the patient gives a history of scarlet fever, tonsillitis, malaria, pregnancy, exposure to cold, etc., we feel satisfied to put the blame on them. Since there are very few people who have not had one or more of the above

diseases, and since it is definitely known that scarlet fever, tonsillitis, malaria, etc., may be followed by acute nephritis, and since acute nephritis frequently is followed by chronic nephritis, the chain of evidence seems fairly well established that these infectious diseases are largely the causative agents of chronic nephritic involvement. In some cases in which we get a history of absolute well-being throughout the entire period of the patient's life, without any history of illness whatsoever, we put the blame on some "noxious poison" or some "product of metabolism" and let the matter go at that.

To my mind this does not at all seem a satisfactory explanation of the cause of nephritis. When we administer small doses of uranium nitrate to animals a severe form of nephritis is set up. It does not attack some and leave out others, but attacks every animal. The same is true for every nephrotoxic substance, be it cantharidin, lead, mercury, tartaric acid, oxalic acid, etc. They all attack the kidneys of every animal that receives the poison. When we see a large number of human individuals develop scarlet fever, some of most severe type, and come out with kidneys unaffected, whereas in others the mildest attack will be followed by nephritis, the same being true for tonsillitis, malaria, pregnancy, exposure to cold, etc., I cannot help but feel that these intoxications play but a secondary role, *i. e.*, merely an exciting role and that the primary seat of trouble lies in the kidney itself. We can readily conceive of organs in the human body at birth being of functional capacity below par. A great many combinations may go wrong during the period of embryonic development, especially during the period of differentiation, giving rise to single organs which may not be equal to the task thrown upon them in later life and which will break under the strain, giving rise to abnormal physiologic function, disease and finally abnormal pathology.²

I remember some years ago talking to Prof. Stockard, of Cornell University, on that very subject. Stockard, who is one of the foremost embryologists in this country, has devoted a great deal of his time to studying prenatal influences on development. He expressed his views at that time, saying that he believed that every person dies from the disease with which he is born. That during the period of differentiation the organ is marked out which is the weak link in the chain. Similar views are accepted now by all students of endocrinology in regard to endocrine disturbances, and one has to ponder only for a few minutes and go over the history of his cases to realize how true and how important that view is. The same view may be applied to cardiac and pancreatic conditions, diabetes, etc.

² I must say here that in my mind it is not at all a solved problem that altered structure precedes altered physiologic function. We must view the body as a chemical factory and we may have altered chemical conditions and altered physiologic results without being able to detect any changes in the cell structure by means of the microscope. For after all, while the microscopic examination of organs is a tremendous advance over the premicroscopic period, from the point of view of cell function it is a hopelessly crude method.

We recognize that we are all born with different degrees of mentality and intellectual capacity. We are also born of different stature and of different capacities for physical strength. Because of these differences we adjust ourselves on different planes in our social structure. These differences we can recognize early in life and do not attempt to force the prizefighter into a professorial chair nor the professor into the ring. We do not, however, look for differences in the functional capacity of the kidneys, lungs, heart, pituitary, thyroid, etc., as long as the individual feels well. Hence they go unrecognized. Any insult in the form of infection, or any strain, as pregnancy, may cause a break in the weak link.

My conclusion, therefore, in regard to the causes of nephritis is, that all the factors usually mentioned, as the etiologic factors, as infection, exposure, pregnancy, autointoxication, etc., are the precipitating causes, but underlying that the patient's predisposition plays the greater role.

If the individual goes on in life without any serious infection or intoxication he may stay well. As he progresses in life the weak organ is the first one to show signs of "old age" and begins to fall behind in its function.

The Physiology of the Kidney. Before we take up the discussion of the disturbances in kidney function that take place in chronic nephritis it will not be amiss to briefly review the physiology of the kidney.

Anatomically the kidneys are composed of a tremendous number of units. Each unit, in turn, is composed of five successive portions:

1. The glomerulus, surrounded by a capsule.
2. The proximal convoluted tubule.
3. The loop of Henle, consisting of a long descending and ascending loop.
4. The distal convoluted tubule.
5. The collecting tubule.

The glomeruli and the tubules are lined throughout their course with epithelial cells, but of different kinds of cells in different parts. In the glomeruli and loop of Henle we find flat endothelial cells, cells similar to those that we find in the walls of the capillaries, where there is the greatest opportunity for interchange of materials between tissue and blood. In the convoluted tubules we find epithelial cells of the type that we find in any secreting gland.

When we were students we were taught that it was the function of the kidneys to excrete urine, *i. e.*, water and all the soluble waste products of metabolism. This is essentially correct today. But now we must look at it from an entirely different angle—not from the point of view of the urine but from the point of view of the body and the blood.

We know that in the blood we have a fluid which is composed of a great many products of intermediary metabolism. We also

know that it is composed of proteins, sugar, lipoids, amino-acids, urea, uric acid, creatin, creatinine, purins, sodium, potassium, calcium, magnesium, iron, carbonates, sulphates, phosphates, chlorides, etc., the concentration of which is kept remarkably constant. We have also learned to know that the kidney exercises a remarkable selective power for its secretions so that these various substances are maintained at definite levels of concentration in the blood.

Take for example the excretion of chlorides. If an individual is on an absolutely salt-free diet the chloride in the blood will remain at a constant level and the kidney will refuse to excrete any of it, and we actually may find urines with merely traces of chlorides. On the other hand, if the person ingests a large amount of chlorides the moment absorption begins and its concentration in the blood tends to rise the kidneys begin to excrete the chlorides, so as to keep its concentration in the blood at a definite level.

The same is true for water, and it is perfectly remarkable with what promptness the kidneys respond to the ingestion of water.

The adjustment of the kidney with regard to glucose is really to be marvelled at. The blood contains normally from 0.08 to 0.12 per cent. sugar. None of it is excreted by the kidney, or if it is, as is claimed by Benedict, it is in such small traces that it can play no practical role. If, however, for one reason or another the glucose concentration reaches 0.13 to 0.15 or 0.18 per cent. the kidneys immediately begin to excrete it so as to lower its concentration in the blood.

Further, the animal body must be considered as a chemical factory in which acids and alkali are being formed all the time, but not to the same extent at different times. At one moment we may have a large production of acid, as during the period of high protein digestion; at the next moment we may have a large amount of alkali formed, as during the period of digestion of vegetables. The former state would tend to render the blood acid, the latter alkaline. The blood, however, under all conditions of health does not vary in its reaction at all: Why? Because the kidneys are adjusted with such sensitiveness to acid and alkali production that the moment one has a tendency to disturb the equilibrium, excretion of it begins immediately. Whether we are awake or asleep, active or inactive, on acid or alkaline diet, the blood will always be kept in what we have chosen to call a normal state of purity. It is the function of the kidneys to keep it thus.

Do you know that it takes a certain amount of salt to keep the globulins of the blood in solution, and what might happen if the globulins were to precipitate out in the blood for lack of that amount of salt? The red blood corpuscles are cells that require certain definite osmotic conditions in the blood for their proper functioning and to prevent them from either shrinking or laking. These conditions can only be maintained by a certain definite water to salt relationship.

The osmotic pressure of the blood is measured by determining the depression of the freezing-point and the extreme variations under all conditions of normal life are only from -0.56° to -0.58° C. It is the function of the kidneys to regulate these relationships and to permit no disturbance whatsoever.

From all this we see that while it is the function of the kidney to excrete urine, of far greater importance is its function in maintaining the proper equilibria in the blood. And from the point of view of understanding what happens in the nephritic individual, this is of the utmost importance.

Until now we have discussed the functions of the kidneys *en masse*, we shall now devote a few moments to a review of the mechanism of urinary secretion.

As was said above, the kidneys are composed of functional units which are made up of glomeruli, distal and convoluted tubules, loops of Henle and collecting tubules. The glomeruli and loops of Henle are lined with flat endothelial cells, whereas the convoluted tubules have epithelial cells of the type that we find in all secreting glands. On the basis of the peculiar funnel-like structure of the glomeruli it was early assumed that the urine was filtered through it by purely physical means. All the experiments today tend to support this view, and it is definitely established that water and salt are excreted mostly through the glomeruli, while the tubules, especially the convoluted portions, excrete most of the nitrogenous constituents like urea, uric acid, creatin and creatinin. The urine as it passes out of the glomeruli is of very low concentration, similar to that of the blood. In its passage through the various tubules water is reabsorbed, so that by the time it reaches the pelvis of the kidney the urine becomes vastly more concentrated than the blood.

Pathologic Physiology in Nephritis. On the basis of the above physiologic considerations we may readily see that any disturbance in the glomerular function will be followed by a disturbance in the water and salt elimination, which means an accumulation of water in the tissues, with edema and general anasarca, depending upon the severity of the case. A patient like this may have no trouble eliminating the products of protein metabolism like urea, uric acid and creatinine.

On the other hand, disturbances in the tubular portion of the kidney will cause interference with the elimination of urea, uric acid and creatinine, while water and salts may be secreted perfectly.

As a matter of fact all the cases of nephritis that we come across belong to one or the other group in their early stages. In their later stages the whole system is likely to break down and there may be interference with both water, salt and nitrogenous elimination.

The tubular type is by far the more common. Of 230 cases of nephritis that I have had the opportunity of studying in the past few years only nine were of the glomerular type. Why the tubular

part of the kidney should be so much more vulnerable is a difficult matter to answer. Perhaps it might be explained on the basis that the tubular cells have more positive work to do in secreting solid substances, like urea, uric acid and creatinine, than do the glomerular cells in passing water and salts. And it is a matter of common knowledge that the least soluble of the three—uric acid—is the first one to fall behind in kidney decompensation and the first one to be found retained in the blood. The tubular cells may become fatigued earlier in life and break under the strain.

The Clinical History of Nephritis. To properly appreciate the development of the clinical history we must bear in mind a few facts:

1. That the amount of kidney tissue that is possessed by any normal individual is much greater than his physiologic requirements, *i. e.*, as far as excreting cells are concerned, we have a large factor of safety. It has been demonstrated that we may remove one kidney completely and a good portion of the second one, and there will be left enough kidney tissue to carry on the normal functions.

2. There are no subjective symptoms and there may be no objective symptoms for a long time after disturbance in the kidney function has set in.

3. That all the symptoms of nephritis are symptoms of deficiency in kidney function.

With these three facts in mind we can readily see why the disease sets in so insidiously, and a patient may go on for years and years developing chronic nephritis without its being detected. It is because of this point that the education of the public to subject themselves to a systematic medical examination at regular intervals becomes of great value. A large proportion of all the nephritic cases that I have seen were first recognized while applying for life or health insurance or by organizations like the Life Extension Institute.

The early history of chronic nephritis is entirely obscure. Symptoms develop only later, and these may vary in different individuals. The earliest cases that I have come across are those that have come to me complaining of having been refused life insurance. These people feel perfectly well and are inclined to discredit the value of the insurance examination. On careful examination I find these patients may have a slight elevation of blood-pressure, 140 to 180 systolic and 75 to 80 diastolic. There may or may not be small traces of albumin and a few casts in the urine. Quantitatively the urinary output is normal, the nitrogen and chloride elimination is perfect, while all the functional tests of the kidney show normal activity. These individuals have absolutely no subjective symptoms whatsoever and the objective symptoms may not always be present. For future reference, we shall designate these cases as belonging to Group A.

The second group of cases are those that have some subjective

symptoms. They come complaining of a tired feeling, especially in the afternoons. They do not feel as ambitious as they used to. They may have frequent attacks of headaches, with momentary dizziness; they may have slight shortness of breath and palpitation of the heart on exertion. Examination shows essentially the same findings as in the case of Group A, except for the fact that the blood-pressure may be higher. We may find here cases with a blood-pressure of 200 and there may be decided left ventricular hypertrophy. The urinary examination may show the presence of fairly large amounts of albumin and a few casts; the great majority have only a small trace or none at all. All the functional tests are normal; the blood examination is normal. We shall call these cases Group B.

To the next set of cases, Group C, belong the vast majority of my cases. Most of their symptoms are referable to the cardiovascular system. They come complaining of frequent headaches, dizziness, palpitation of the heart and shortness of breath on the slightest exertion, dark spots in front of the eyes, insomnia, anorexia, edema of the legs, puffiness under the eyes, ringing in the ears, pain in the precordium, etc. On examination these patients are found to have systolic blood-pressure anywhere from 180 to 280 and diastolic from 80 to 150. The great majority of them show a good myocardium, with hypertrophied left ventricle, while a number of others show decided evidence of failing myocardium, the symptoms depending, of course, upon the degree of cardiac insufficiency.

To the last, Group D, belong all those cases of nephritis which show unmistakable signs of kidney deficiency or decompensation. Whether it be poor water and salt elimination with edema, poor phthalein elimination or retention of nitrogenous products in the blood. They show signs of intoxication of varying severity and are mostly bedridden. As a group they give the impression of being very sick. They may have gastric disturbances like anorexia and vomiting. In the later stages they may develop a peculiar urinous odor. As a rule they have all kinds of complications, especially in the cardiovascular system. There may be nervous and mental symptoms, varying in degree from severe headaches, insomnia, neuralgic pain, retinitis, diplopia, temporary blindness, etc., to full-fledged attacks of irrationality, convulsions and coma. Examination of the urine will show the presence of large amounts of albumin and casts. The quantity of urinary output may vary and may depend largely upon the degree of cardiac complication.

We may therefore, in view of the above, recognize four degrees of severity in the course of chronic nephritis.

Group A. In which the patient has no subjective symptoms whatsoever, and not very marked nor permanent objective symptoms.

Group B. In which the patient has slight subjective symptoms, usually referable to cardiovascular disturbances, and the objective symptoms more marked and more permanent.

Group C. In which the patient has fairly severe subjective symptoms and the objective findings of nephritis are quite marked. Functional tests still show normal elimination of known products of metabolism.

Group D. In which the patient shows the first unmistakable signs of kidney functional break-down or decompensation, with severe cardiovascular or nervous symptoms and the beginning of uremic symptoms.

Diagnosis of Chronic Nephritis. The diagnosis of chronic nephritis in the later stages or when albumin or casts are present is a very simple matter. The difficulty, however, is presented by those groups of cases which have negative urinary findings, *i. e.*, no albumin and no casts, and still show a great many of the symptoms that we find in chronic nephritis, namely, high blood-pressure, cardiac hypertrophy, arteriosclerosis, retinitis, etc. A certain school of clinicians are inclined not to connect these cases with nephritis but to put them in a class by themselves as cases of essential hypertension.

We all know that we may have severe cases of chronic nephritis, with a tremendous amount of interference in kidney function and only traces of albumin. We also know that we find large amounts of albumin in urines of individuals who never have more than a mild type of kidney interference. In other words the amount of albumin in the urine, and for that matter, also, the number of casts in the urine, are in no way criteria of the severity of the case. If the slightest trace of albumin is detectable in any case of hypertension, even the greatest enthusiast of the essential hypertension idea would diagnose it as nephritis. Are we justified, then, in the absence of those traces of albumin, in disconnecting cases of hypertension from chronic nephritis, especially so, when we know it as a fact, that every case of hypertension, if it does not suffer a cardiac break-down or cerebral hemorrhage, will ultimately show unmistakable signs of severe nephritis, and when these do develop, the course to the final break and uremia is a very short one indeed.

Chronic nephritis, high blood-pressure and hypertrophied heart cannot be separated from one another. They are a series of links in a closed chain, forming a complete circle, and at the present stage of our knowledge we cannot say definitely whether the chain begins here and ends there. There are just as many arguments in favor of its beginning there and ending here. The question whether chronic nephritis is the cause of high blood-pressure or whether high blood-pressure is the cause of nephritis should be left open, and from the point of view of protective therapy, I personally am inclined to consider every case of hypertension as a potential case of chronic nephritis, just as I am inclined to consider every case of nephritis a potential case of uremia.

We have made enormous progress in the study of the chemistry

of the blood and in the study of nephritis from the point of view of the blood. But can anyone say that we have completely exhausted the field and that we know every substance that is present in the blood which should have been excreted by the kidneys? We cannot. There may be any number of substances retained by the kidneys which will account for a rise in the blood-pressure.

Take, for example, gout. Who would have believed, fifty years ago, that the uric acid accumulation in the blood was due to the failure or difficulty on the part of the kidneys to excrete it? But this is the case, and from the modern point of view it may be considered a specific form of nephritis which in the great majority of cases develops ultimately into ordinary nephritis.

That we find peculiarities in different individuals with apparently normal kidneys in regard to their power to excrete different substances we know from different sources. We know, for example, that some kidneys will excrete sugar when the blood sugar concentration is only 0.10 per cent., while others will not excrete it even when the concentration reaches 0.26 per cent. The latter is certainly "nephritic" as far as sugar is concerned. Idiosyncrasies to drugs like bromides, iodides, arsenic, etc., may also be explained on the basis of specific failure to eliminate those substances.

On the basis of all the above, I would therefore suggest that chronic nephritis should not be diagnosed alone on the basis of the presence of albumin and casts—these are too unreliable—but on the basis of the general clinical findings. And it is safer, as far as therapy is concerned, to diagnose a case as of potential chronic nephritis than of essential hypertension.

Prognosis of Chronic Nephritis. The ability to prognosticate the outcome of any disease is a skill which takes years of experience to acquire. It is not one which can be transmitted from master to pupil. It is not like science, that can be learned, but more like art, acquired from within by intuition. A good prognosticator is one who has a faculty for correct judgment, a thorough realization of the patient's condition and the ability to detect in advance possible complications that may set in and their effects upon the patient, plus a vast experience with a large number of cases of a similar nature.

Prognosticating practically means prophesying, and one knows what the world thinks of prophecies that prove false. The patient, and particularly his family and friends, are very much concerned with the course of any disease and expect the physician to tell them the outcome. One's wisdom must receive a terrible jolt after pronouncing a bad prognosis and declaring a patient hopeless and sure to die, to meet him months or years later and be reassured of the "bad" prognosis. It is equally unpleasant to hear of the patient's death after having made optimistic prognoses.

Anything, therefore, which tends to transfer prognosis from the

plane of art, guesswork or speculation to that of science, will mean a tremendous step forward. Fortunately for us in the field of nephritis a step like this has been made during the past ten years, and we may add here, with not a little pride, that most of the work was developed in our own country.

The course of the disease in nephritis depends entirely upon the functional capacity of the kidneys, and by determining that we can foretell with a fair degree of accuracy, what the result will be. Of course, we must ever be mindful of the fact that with chronic nephritis we do not deal with kidneys alone but with a myocardium which may suffer insufficiency and with cerebral arteries which may rupture—all of which may upset our conclusions and direct the patient's course into different channels.

The Functional Tests in Nephritis. There are three functional tests that we employ today, each of which has its special advantages.

1. In the first test we administer certain substances to the patient and study the speed with which it is excreted by the kidneys in the urine. Most of these substances are foreign to the body. These are potassium iodide, lactose and phenolsulphonephthalein. Of these the last one is the easiest to carry out and gives a fairly reliable indication of the condition of the kidney.

In the morning, before breakfast, the patient is asked to empty his bladder. He is then given 400 c.c. of water to drink to ensure free diuresis; 1 c.c. of phenolsulphonephthalein solution, containing 0.006 gram of the drug, is then injected intramuscularly in the lumbar region and the time noted. Exactly one hour after the injection the patient is asked to void urine in a cylinder and is given another 400 c.c. of water to drink. At the end of the second hour he is asked to empty his bladder again. To each cylinder of urine a small amount of concentrated sodium hydroxide solution is now added, which brings out the purplish-red phthalein color and the volume of each specimen is brought up by adding water to 1000 c.c. The color of a small sample of this is now matched up with a standard solution and the percentage of phthalein excreted calculated.

A kidney that has sufficient functioning cells to carry on the required excretion of the products of metabolism will excrete not less than 35 per cent. of the phthalein during the first hour and about 20 to 25 per cent. during the second hour, a total of 55 to 60 per cent.

Cases belonging to Groups A, B, and C give normal phthalein figures. Although in Group C we may meet with cases of advanced nephritis, still we will get normal phthalein elimination because there are enough functioning cells left to carry on the work. The prognosis for the immediate future, as far as the kidney is concerned, is good. Of course before making this prognosis one must be circumspect of the cardiovascular condition of the patient. If the blood-pressure is moderately high, say about 200 systolic and about

90 to 110 diastolic, with a heart that is not irritable and only moderately hypertrophied, the prognosis is good and may continue to be good for quite a long time. If the blood-pressure is around 250 or over and the diastolic pressure is around 130 to 150 the outlook is not so good. For some reason or other high diastolic pressure invariably presages myocardial trouble. Frequent attacks of palpitation of the heart in this stage is another unfavorable sign in determining the prognosis.

When we find only 45 to 40 per cent. of phthalein elimination in the two hours it means that the kidneys are beginning to fall behind in their work, which is a very serious matter. It means the patient's entrance into the Stage D of the disease. We must therefore be very careful that no extraneous influence has affected our results. It sometimes happens in men with enlarged prostates and in women with prolapse of the uterus and cystoceles that not all of the urine secreted by the kidneys in a given time is actually voided. During the two hours more phthalein will be excreted by the kidneys than is delivered by the patient into the cylinder, because a considerable portion is retained in the bladder. It is therefore important to repeat the test when low results are obtained, catheterizing the patient at the end of the second hour and washing the bladder out with distilled water.

If on repeated tests the phthalein output is low the prognosis is very serious. While a patient may have nephritis throughout practically his entire life, and I have seen cases of nephritic histories of more than thirty years' duration, a patient cannot live very long with a decompensated kidney. Once the kidney begins to fall behind matters soon get beyond one's control. Once the patient has broken through into Stage D the phthalein output will keep sinking until a condition is reached in which there is no output at all. Of course you must realize that the downhill course is not in a straight line. There may be temporary improvements, because so much of the kidney function at this stage is dependent upon ups and downs in the circulatory apparatus. But on the whole the outlook is very grave both for the immediate and ultimate future.

In the phthalein test we find a ready and quick method of orienting ourselves as to the patient's functioning capacity. It requires simple apparatus, little expense and above all very little discomfort to the patient.

The second functional test is made by a quantitative study of the urinary output. This was first suggested by Schlager and Hedinger and developed in great detail by Mosenthal and his coworkers. For the past few years I have worked on this method and succeeded in modifying it.

The test as it is carried out is based on the following consideration: If we collect the urine of any normal individual for twenty-four hours in two twelve-hour portions, starting the first twelve hours

at 8 A.M. and closing it at 8 P.M., and the second 12-hour period from 8 P.M. to 8 A.M. the following day, taking care the individual has his principal meal in the daytime, supper at 5 P.M. and does not eat or drink after that until the following morning, we find that the relationship of day excretion to night excretion for nitrogen is roughly 3 to 2 and for chlorides it is 3 to 1 or 4 to 1. The nocturnal water output will be, as in Mosenthal's results, less than 400 c.c. The reason for this is the following: A normal individual ingests most of his food during the twelve hours of the day. As quickly as the products of digestion become absorbed and metabolized the products of metabolism, like urea, uric acid, chlorides, etc., enter the blood stream. As their concentration in the blood increases the kidneys begin to excrete them in the urine. Normal kidneys respond so promptly that comparatively little is left for the night excretion. Therefore do we have a comparatively low nocturnal water output, and the ratio of day to night elimination of solids is as given above.

If, however, the kidneys do not respond so promptly and begin to fall behind in their work some of the material which in a normal individual would be excreted during the day is eliminated during the night, and the proportion of day to night chloride and nitrogen excretion will tend to approach each other. There will also be nocturnal polyuria, because with the excretion of more solid materials during the night there is also excreted a larger amount of fluid.

By morning all the nitrogenous products from the blood are excreted, and if we examine the blood then it will be found normal in its nitrogen products concentration.

We can thus see that by studying the shifting of the day to night ratios in the nitrogen excretion we can detect an approaching kidney insufficiency long before the blood figures change.

This method has advantages over the phthalein test because in addition to giving information of the degree of kidney function it also gives us an idea of the special interference—whether it is water, chlorides or nitrogenous material that is excreted with difficulty. And from the therapeutic point of view, this is of much greater value.

The third test for kidney function consists of examining the blood for products of metabolism, which are normally found in very small quantities, and which are found very much increased in cases of renal insufficiency. These are urea, uric acid and creatinin.

The blood of a normal individual in the morning before breakfast contains not more than 3 mg. of uric acid, 20 mg. of urea nitrogen and 2 mg. of creatinin per 100 c.c. of blood. In renal insufficiency when the kidney first begins to fall behind in its work, the uric acid is retained first, doubtless due to its insolubility, which gives the kidney the greatest difficulty in excreting it. The figures mentioned above (3 mg.) are the upper normal, and any figure above that is already of grave diagnostic importance. Next to the uric acid the

urea nitrogen begins to climb and may reach to 150 and more milligrams per 100 c.c. of blood. Lastly, the creatinin begins to rise, and when we find creatinin concentration go up to 5 mg. per 100 c.c. of blood the case is absolutely hopeless and death from uremia is imminent. I know of only one case that lived with high creatinin in the blood for some time. All others succumbed within a very short time.

I should like to say here, in passing, that the results of these methods are of the utmost importance. The chemical procedure has been worked out carefully, and it takes careful and skilled chemists to make these determinations, so that they will be of value. When entrusted to technicians who know only the motions and do not understand what they are doing, apparently conflicting results are frequently obtained.

The Treatment of Chronic Nephritis. The treatment of a disease like chronic nephritis, in which we can find no one definite cause to remove and for which we have no specific remedy, offers exceedingly great difficulties. Our treatment must be directed along three channels: (1) To ameliorate the patient's symptoms and to make him comfortable; (2) to attempt to check the progress of the disease; (3) to prolong the patient's life.

You will recall that in the early part of our discussion I described four stages of severity in the clinical course of chronic nephritis. In Stage A I placed all those cases that have no subjective symptoms whatsoever but have some objective symptoms which are not very marked nor permanent.

The cases I have seen belonging to this stage are not very numerous, about 20 in all. Those who are engaged in the general practice of medicine have the opportunity of discovering them. I use the word "discover," because they come to you for other reasons, not being aware of the existing renal involvement. A great deal can be done for these people at this stage which cannot be done later.

A great deal of tact must be used in announcing to a perfectly well-feeling young man or woman, at the height of their careers, that they have some renal involvement or high blood-pressure. It is a terrific shock to the great majority of the patients. Most people immediately associate it with the worst complications and early death; neither of which is correct. I consider it a terrible crime to tell a patient with high blood-pressure that the bloodvessels in his brain are likely to burst any moment or that he is sure to die in a few months or years. Patients with chronic nephritis and high blood-pressure have been known to live to a good old age. I have one patient, a woman past seventy years, who was treated by the elder Dr. Janeway for some twenty years for her blood-pressure and kidneys. Then she was a patient of Theodore Janeway's, and I have had her under my care for the past five years. Her blood-pressure is never below 220 and very frequently around 280. She

takes good care of herself and has lived a long and useful life in spite of her physical limitations.

The early recognition of these conditions is of the greatest importance—not because these patients require early treatment. No. They require no treatment at all, and the more we let them alone the better. But because it is of great importance that they learn to rearrange their mode of living. To be moderate in all their habits; not to overeat; not to overdrink; not to overwork; not to subject themselves to unnecessary excitement; not to engage in violent exercise, etc. It will not do for a young man, aged thirty years, with a blood-pressure of 160 to 170, to be engaged in a work which will keep him running up and down stairs. Nor will it do to have a man in a similar condition, with decided evidence of renal lesion, engaged in work in which he is continually exposed to drafts and extreme changes of temperature. It is our duty to explain to those people, and to make them realize, that while they have a physical limitation, with care they can live out their lives, and that it is in their own interests to quickly adjust themselves to their condition. It is indeed a hardship for a father of a family to have to throw up his work and seek a more sedentary occupation, but this is the time to do it and not when it is too late.

The patient's gainful occupation and his physical condition are very intimately related, and we clinicians must enter into that phase of the patient's life. We must take it upon ourselves to convince the patient of the advisability of making the change if we feel that his work is injurious to his health and we feel assured that the change will benefit him.

I consider the rearrangement of a patient's social status to his physical condition the greatest step toward preserving his health and prolonging his life. Next comes the regulation of his habits of eating, drinking and smoking. We must also inquire into the patient's mode of spending his leisure time and into the number of hours he spends in sleep. Restful hours and plenty of sleep add a great deal to the patient's well-being.

It is also important at this stage to look after the general hygienic condition of the patient, to teach him to look after the regulation of his bowels and the condition of his teeth and tonsils. When the patient's functional capacity of the kidney is good there is no necessity for restricting the diet too much. He can have an amount of protein corresponding to about 10 to 12 grams of nitrogen per day. I usually advise the elimination of all meat soups and excessive salt from the diet. There is a feeling in the profession that eggs are harmful to nephritic patients. This is not so. Eggs for the nephritic are as healthful a food as for any other patient.

With the exception of a possible dose of bromides, to help tide over the nervousness caused by the disturbance in the patient's life, it is not advisable to use any medication at this stage.

I have seen patients at this stage fed on lithia tablets, nephritic pills, nitrites, diuretics, alkali and what not. We should realize what these patients need at this stage. The circulation is good, the kidney function is good—why disturb them? Why give them alkali to excrete and thus throw extra burdens on the kidneys? Why give them diuretics and drive an already tired organ? The more the patient is let alone the better.

What was said for patients of Stage A is equally true for patients of Stage B. We are not dealing with people that are sick but with people who suffer a physical handicap. Our chief duty now lies in preventing the patient from doing things which might hasten a breakdown. If he develops slight edema of the ankles, or if the blood-pressure runs up too high, it may be advisable to place him in bed for a week or two. It is remarkable what a tremendous effect this has on the patient. I have seen cases with blood-pressure of 220 and 240 come down to 160 and 180 after spending only one week in bed. The use of nitrites in these cases is of absolutely no use, except if the patient has anginal attacks. In that case I give him 1 grain of sodium nitrite or $\frac{1}{50}$ grain of nitroglycerin. The use of benzyl-benzoate, recently advised by Macht is of no use whatsoever.

Before prescribing a drug to a patient with nephritis it is advisable to know what one wants to accomplish, what symptom or group of symptoms one wishes to eliminate and to watch for the effect. If we do get a response, stop the drug immediately. If we do not get any improvement, continuing the drug will not help but may introduce serious complications. I remember 2 cases, 1 in private practice and 1 in the hospital, that I was called in to see. Both patients had high blood-pressure, with albuminuria and casts. The history of both was that for the past few days they had been getting more and more stuporous, until finally they could hardly be aroused. The diagnosis of uremia was made in both cases. From both the examination and the general history one could hardly come to any other conclusion, but on examining the blood we found its chemical composition normal, save for a slight increase in the uric acid. As we shall see later, patients with uremia never have normal urea nitrogen. The diagnosis of uremia had therefore to be abandoned. It was then brought to light that both patients had been taking chloral hydrate for several weeks. I felt convinced that the chloral hydrate was responsible for the complications. Several days' abstinence from the drug cleared up both cases. Both patients are alive today.

We must ever be mindful of the fact that most drugs have to be excreted from the body and that it is done very largely by the kidneys. Therefore it is important when drugs have to be used to select only those that cannot possibly aggravate matters and introduce complications.

There are a great many patients who believe that the "albuminuria" or the "high blood-pressure" constitutes their illness, and they expect the physician to "cure" them of it. A fifteen minutes' talk, in which the whole matter is explained to the patient and brought within his mental grasp, will save a lot of trouble in the end.

Success in the treatment of such a condition depends not upon drugs or medicine but upon teaching the patient to recognize his limitations, to save himself every bit of unnecessary exertion, to readjust his activities, to regulate and moderate his diet, to spend as much of his time at rest as possible. In other words, to teach the patient to live within his physiologic means.

Patients who are classified as belonging to Group C are mostly ambulatory, still engaged in gainful occupations, but who begin to find it a great burden to get through the day's work. They suffer primarily from symptoms affecting the cardiovascular and nervous systems. As far as the kidney function is concerned there is still perfect elimination of all the known products of metabolism, though in the later stages there may begin evidences of delayed excretion.

The treatment is entirely symptomatic. Headaches, dizziness, palpitation of the heart and shortness of breath form the chief complaints of most of the patients in this stage. Seldom will these symptoms be manifest in patients who have a blood-pressure of less than 220 or 240. When this does occur the patient's myocardium is usually at fault. Obesity may also frequently be responsible for it when accompanied by a not too strong myocardium.

The best and most efficient remedy, and one which seldom fails, is one or two week's vacation in bed, with a dose of bromides, 15 grains three times a day. During this period I restrict the diet to a low protein, low salt and low purins, *i. e.*, cut out meat soups, tea and coffee. In addition, I also restrict the absolute amount of food. If the headaches and dizziness are very severe the use of cinchophen tablets, in 7-grain doses, two or three times a day, is frequently of great benefit. Tolysin in 5-grain doses may also be used. The latter has the advantage of being tasteless and does not tend to produce gastric distress. Phlebotomy and withdrawal of 300 to 500 c.c. of blood is frequently followed by relief. I have had several patients who suffered such intense headaches that nothing but morphin could relieve them. The performing of a lumbar puncture and withdrawal of some of the spinal fluid plus a venesection brought them considerable relief, and they were able to get along without drugs for a long time afterward.

Staying in bed, free from excitement and business worries, has positively the most soothing effect on a patient. He gets a new lease of life and feels better for months afterward.

I usually prescribe the following diet during this period of rest:

Breakfast:

Stewed fruit.

Cereal and milk.

1 slice of bread and butter.

$\frac{1}{2}$ cup of milk, hot water and sugar.

Lunch:

Cream of celery, cauliflower or tomato soup.

Rice cakes, potato cakes or pea croquettes.

Green vegetables.

Salad: lettuce, tomatoes, olives, with olive oil.

1 slice of bread and butter.

$\frac{1}{2}$ cup of hot water and milk.

Dessert: puddings, custard or ice-cream.

Supper:

The same as breakfast.

If hungry between meals, half a glass of zoolac or fermilac.

When the patient returns to business it is not necessary to have the diet as strict as this. As long as there is no sign of retention I allow meat, poultry and eggs to such an extent that the urinary nitrogen does not exceed 10 to 12 grams per day. This is a comfortable diet and allows plenty of variety.

Breakfast:

Fruit of any kind.

Cereal with milk or cream.

Bread and butter.

Milk, Kaffee Hag or Postum.

Lunch:

1 or 2 eggs.

Fruit salad.

Bread, butter and milk.

Dessert: custard, puddings or ice-cream.

Dinner:

Milk soups.

Fish or meat—1 or 2 ounces.

Vegetables of all kinds.

Salads.

Bread and butter and milk.

Desserts.

The patient is advised to use salt and pepper and other condiments in great moderation. The use of alcohol in small doses, in dilute form at infrequent intervals, is not to be objected to if it agrees with the patient.

Variety in diet is very important, for if they do get the same thing they will soon tire.

Edema of the legs is a very frequent complaint at this stage. It

usually comes on in the afternoon and passes away overnight. I know of nothing that works so surely for its eradication as rest in bed.

It is well to warn patients in this condition of some of the complications that may beset them and which may prove to be of great danger to them: (1) Upset stomach, with vomiting; (2) constipation and the habit of straining at stool; (3) catching cold, with developing attacks of coughing. Every one of these is preventable if the patient will only take care.

Cardiac complications are very common at this stage and very frequently the patient will suffer from various degrees of cardiac dilatation, with relative mitral and aortic regurgitations. This is very serious and invariably affects the course of the nephritis very adversely. The kidney function depends entirely upon a perfect and proper supply of blood. A perfectly normal kidney's function may be arrested if the blood supply is interfered with. Think of what must happen to the struggling cells of a degenerated kidney when the blood supply becomes irregular and incomplete! We frequently find marked oliguria develop, and if the patient should happen to be drowsy, or unusually irritable, irrational or perhaps have some convulsive seizure, the diagnosis of uremia is frequently made. I take this opportunity of calling your attention to one thing, namely, that we must reserve the term uremia specifically for those cases in which we have renal insufficiency, with retention of the products of metabolism in the blood. Uremia should not be diagnosed on the basis of the clinical symptoms but on the basis of the blood findings. Dozens of times have I seen uremia diagnosed on the basis of clinical symptoms without corroboration by blood findings and events proved later that uremia was not the cause of the complex.

Oliguria and nervous symptoms in nephritis, with cardiac decompensation, do not always mean uremia, unless it is associated with a marked increase in the uric acid, urea and creatinin concentration of the blood. If this is not the case the heart is the primary offender and the patient should be treated vigorously with digitalis and the other known cardiac stimulants. In no case of chronic nephritis have I seen any benefit gained by the use of diuretics, like diuretin, but when oliguria is due to cardiac decompensation the effect of diuretin is simply marvellous. The administration of 20 grains of that drug two or three times per day may convert a 200 c.c. urinary output per twenty-four hours into an output of 2000 c.c.

A word about the acidity of urine and its concentration in cases of cardiac insufficiency: I have seen physicians worry a great deal about it and frequently prescribe alkali, sodium bicarbonate, in rather large doses, which frequently upsets the stomach and brings on attacks of vomiting and also diarrhea, with gas distention of the

intestines, etc. The truth of the matter is that the acid in the urine does no harm to the patient. The blood alkalinity, measured by the carbon dioxide capacity, is usually normal in those cardiac cases. As far as the concentration is concerned it is bound to be high, for in those 200 c.c. the patient will excrete practically all of the nitrogenous matter. Water and salts are the only substances that are held back in cardiac decompensation, that is why those cases have severe edema and general anasarca but no uremia.

If alkali must be given it is wise to give it in small doses—5 grains, or at most 10 grains, at a time.

We shall now take up the treatment of the last stage of nephritis, namely, Stage D. Unfortunately this is a thankless task. We are dealing with a group of people who no longer possess enough functioning cells in their kidneys to excrete the normal products of metabolism. The result is that these products tend to accumulate in the blood. The human individual metabolizes three kinds of foodstuffs, carbohydrates, fats and proteins in addition to salts and water. The products of carbohydrates and fats are carbon dioxide and water. The former is excreted by the lungs, the latter by the kidneys. The products of protein metabolism are urea, uric acid, creatinin, amino-acids and a number of other substances, which can be excreted only by the kidneys. A normal individual must receive a certain amount of protein to maintain himself in protein equilibrium. The patient in Stage D cannot receive that amount of protein. He must be kept on a protein level commensurate with his ability to excrete nitrogen, and as the latter sinks the intake must be diminished. As far as nutrition is concerned, everything must be subordinated to the patient's renal capacity or else collapse is inevitable.

Some of these patients have very violent symptoms, others are more fortunate. In either case the outlook is very grave. The treatment depends largely upon the symptoms and should also be directed toward helping the body rid itself of the retained products and preventing the accumulation of new products.

If the patient has difficulty with water and salt elimination edema will be the most prominent feature of the symptoms. Salt-free diet and restricted water intake are absolutely essential. Everything must be cooked or baked without salt. If the nitrogenous excretion is good I allow them sufficient protein. On such a diet the edema will gradually improve. The use of diuretics is absolutely contra-indicated. We may get an increase in the water output for a day or so, and after that it is worse than before. Digitalis may be of help, probably because it spurs up the heart, and should be used, cautiously. Frequent purgation, by means of salts of magnesia, is of great value. Diaphoresis may also be of service if not overdone. Hot packs, hot air baths or electric baths are good remedies. Many

of these people perspire only with difficulty. In that case it is important to watch them carefully when in the hot box. Unless they begin to perspire I have them removed, because the intense heat may cause a rise in the body temperature and a heat stroke follow. I do not, as a rule, advise the use of diaphoretics, but if the patient cannot perspire a small dose of pilocarpin hydrochloride, $\frac{1}{10}$ of a grain, may be sufficient to start perspiration.

The type of nephroses that Epstein has described has nothing to do with the type that we are discussing here, and it does not come under the same category. They are differentiated by having marked lipemia with very high cholesterol in the blood. He claims remarkable results by keeping them on a high protein diet. Personally I have never come across a case in which the edema improved by high protein except where the chloride and salts were restricted. Dr. Christian's experiences in Boston have been similar to mine.

On the whole the edematous patients are comfortable and do not have any of the violent symptoms that we meet in the uremics. They may get fluid in the peritoneum, pleura and pericardium and usually die of secondary cardiac embarrassment or edema of the lungs.

The patients who have difficulty with nitrogen elimination usually run a stormy career, with violent headaches, nausea, vomiting, all kinds of nervous symptoms, varying in degree from restlessness and insomnia to absolute irrationality and coma. They may also have disturbances in the special senses, with diplopia, temporary blindness, retinitis, retinal hemorrhages, etc.

Bromides, chloral hydrate, cinchophene and sodium salicylate help control the symptoms tremendously. Venesection is of great value, and so is lumbar puncture.

In the later stages when coma has set in we very frequently get satisfactory results by doing a venesection, withdrawing 300 to 500 c.c. of blood, followed by a glucose infusion of 300 to 500 c.c. of a 5 to 6 per cent. solution.

Diaphoreses and purgation are also of great value.

The treatment of uremia at best is hopeless. All we can do is to delay the inevitable. Once the diagnosis of uremia is made it spells the patient's death sooner or later, usually sooner.

Therefore do I repeat what I said before: I consider every case of hypertension a potential nephritic, and every nephritic a potential uremic, and treat the uremia, not when it is with us and we are helpless, but months and years before, when we have every facility for its prevention.

TREATMENT OF TETANUS.

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City Hospital.)

LARGE doses of antitoxin have been rather commonly used in the treatment of tetanus. By reporting four consecutive cases which recovered following the use of large amounts of antitoxin intravenously, it is hoped to emphasize the value of this form of treatment.

The routine procedures adopted follow very closely those used by Woolf¹ in reporting a successful case.

1. Antitoxin is given in dosages of 10,000 to 20,000 units, intravenously, several times daily until all spasm is gone.

2. Morphin hypodermically and chloretone by rectum are given every four to six hours during the stage of reflex hyperexcitability.

3. Liquid nourishment and large amounts of water are given every two hours.

REPORT OF CASES.

CASE I.—G. B., male, aged forty-three years. Admitted May 28, 1919.

Complaint. Abdominal pain and cramps.

Present Illness. Three weeks prior to admission he ran a splinter of wood in his finger. One week later he noticed stiffness of his jaw. Stiffness gradually extended to neck, arms, legs and abdomen.

Physical Examination. Temperature, 101.3°; pulse, 120; respiration, 28.

Patient restless and perspiring freely. Jaw muscles spastic and teeth can be separated about three-quarters of an inch. "Risor sardonicus," marked rigidity of neck, arm, leg and abdominal muscles. Tendon reflexes exaggerated. No pathologic reflexes. Marked reflex hyperexcitability.

Treatment. Routine procedure as above. Morphin, gr. $\frac{1}{6}$; chloretone, grs. xx every six hours.

Antitoxin. May 28, 10,000 units intravenously twice; 3000 units intramuscularly.

May 29, 30, 10,000 units intravenously twice.

May 31, 10,000 units intravenously three times.

June 1, 2, 3, 10,000 units intravenously twice.

June 4, 5, 6, 7, 11, 10,000 units intravenously once.

June 14, 15, 25, 10,000 units subcutaneously once.

Total antitoxin, 213,000 units.

June 25, discharged cured.

¹ Woolf: Jour. Am. Med. Assn., 1919, lxxii, 1266.

CASE II.—E. C., male, aged eight years. Admitted October 8, 1919.

Complaint. Stiffness of jaws and convulsions.

Present Illness. About one month prior to admission the child had gone barefoot and had stubbed its toe, leaving a slight abrasion which healed in about a week. Six days before admission he noticed stiffness of jaw, neck and back. On October 7 he had several convulsions.

Treatment. Routine as above.

Antitoxin. October 8, 30,000 units intravenously.

October 9, 10,000 units intravenously three times.

October 10, 10,000 units intravenously twice.

October 11, 10,000; 15,000 units intravenously three times.

October 12, 10,000 units intravenously three times.

October 13, 15,000; 20,000 units intravenously.

October 14, 20,000 units intravenously twice.

October 15, 16, 20,000 units intravenously three times.

October 18, 20,000 units intravenously twice.

October 19, 20, 20,000 units intravenously three times.

October 21, 10,000 units intravenously three times.

October 22, 10,000 units intravenously twice.

October 23, 24, 10,000 units intravenously.

October 25, 10,000 units; 20,000 units intravenously.

October 26, 27, 28, 29, 10,000 units intravenously twice each day.

October 30, 31, November 1, 10,000 units intravenously once each day.

November 1, developed urticaria.

November 27, discharged cured.

Total antitoxin used 755,000 units.

I am indebted to Dr. Blankenhorn for taking charge of this case and also for the use of a syringe outfit by means of which a small needle can be inserted into a vein, and the antitoxin, together with a small amount of saline, injected under pressure.

CASE III.—A. B., female, aged eight years. Admitted June 23, 1919.

Complaint. Stiff jaws.

Present Illness. Two weeks prior to admission the patient ran the point of an umbrella into her foot. Three days ago she suddenly became stiff all over and was unable to chew her food. The day before admission she had a convulsion.

Physical Examination. Temperature, 100.2°; pulse, 128; respiration, 26.

General rigidity; marked "risor sardonicus;" hyperactive reflexes; exalted reflex excitability.

Treatment. Routine procedure as above.

Antitoxin. June 23, 25,000 units intravenously.

June 24, 10,000 units intravenously twice.
June 25, 10,000 units; 5000 units intravenously.
June 26, 5000 intravenously; 15,000 units intravenously.
June 27, 10,000 units intravenously.
June 28, 10,000 units intravenously.
June 29, 15,000 units intravenously.
June 30, 15,000 units intravenously.
July 1, 12,000 units intravenously.
July 2, 15,000 units intravenously.
July 4, 5000 units intravenously.
July 6, 5000 units intravenously.
July 8, 5000 units intramuscularly.
July 10, 5000 units intramuscularly.
July 13, 5000 units intramuscularly.
July 16, 5000 units intramuscularly.
July 19, 5000 units intramuscularly.
July 23, 5000 units intramuscularly.
July 31, discharged cured.
Total antitoxin, 189,000 units.

CASE IV.—J. N., male, aged ten years. Admitted April 25, 1920.
Complaint. Sore and stiff foot.

Present Illness. Twelve days prior to admission the patient ran a nail into his foot. Nine days later the foot began to feel stiff and sore. On the day of admission his jaw became stiff and he had a convulsion.

Physical Examination. Temperature, 101°; pulse, 120; respiration, 30.

Muscles generally hypertonic, with a tendency toward opisthotonos. Jaws can be separated about one-half inch. Profuse perspiration. Marked "risor sardonicus." Deep and superficial reflexes exaggerated. Reflex hyperexcitability. No pathologic reflexes.

Treatment. Routine as in preceding case.

Antitoxin. April 25, 20,000 and 10,000 units intravenously.

April 26, 15,000 and 5000 units intravenously.

April 27, 15,000 units intravenously.

April 28, 15,000 units intravenously.

April 29, 15,000 and 18,000 units intravenously.

April 30, 20,000 and 20,000 units intravenously.

May 1, 20,000 units intravenously.

May 2, 10,000 units intravenously.

May 18, 5000 units subcutaneously.

May 23, discharged cured.

Total antitoxin, 188,000 units.

Discussion. Statistics. While it is the general opinion that antitoxin is of great value in the treatment of tetanus, it is extremely difficult to draw any definite conclusions as to dosage

or mode of administration from published statistics. The most comprehensive figures are those for the cases treated in the British Home hospitals during the years 1914-1917. These tables, compiled by Bruce,² and Cummings and Gibson,³ were carefully reviewed by Ransome⁴ and Golla,⁵ who agree that no reliable conclusions as to the value of antitoxin can be drawn for the following reasons: (1) Prophylactic treatment modifies the disease by lengthening the incubation period which varies inversely with the mortality rate; (2) no attempt was made to standardize the size of dose, the method of administering or the promptness of treatment. For example, some of the cases reported by Bruce were as follows:

	No. of cases.	Mortality rate.
1914-1915	231	57.7
1916	100	31.0

It is impossible to be sure whether the lowered mortality rate was due to more efficient prophylaxis or because more antitoxin was used in the later series. However, clinically, the serum must have made a favorable impression, for in 1917 the British War Office ordered that 50,000 to 100,000 units be injected within the first few days after symptoms appear.

Method of Administration. Sherrington⁶ has reported some experiments regarding the relative value of different routes in giving antitoxin. Monkeys were injected with eight times the lethal dose of tetanus toxin intramuscularly, and in forty-two to seventy-eight hours, tetanus antitoxin, 20 units per kilo, was injected with these results:

	Mortality rate, per cent.
1. Subcutaneous	92
2. Intramuscular	88
3. Intravenous	72
4. Intrathecal	44
5. Bulbar intrathecal	48
6. Cerebral subdural	100

These results would tend to show that for a given dose of antitoxin the intrathecal route was the most efficacious. However, at best, the mortality rate was very high and the results throw no light on the effect of the maintenance of a high concentration of antitoxin in the tissues by repeated injections.

Mode of Absorption of Tetanus Toxin. It is well known that tetanus toxin has a marked affinity for nerve tissue while the peripheral motor nerves have been proved to be the pathways by which it is conducted to the central nervous system. However, on experimental evidence there has been a controversy as to whether the toxin is conducted by means of the axis-cylinders or by the neural and perineural lymphatics. From a therapeutic standpoint it matters greatly as to which of these absorption paths is correct,

² Lancet, March, 1919, i, 9.

⁴ Ibid., December 2, 1917.

⁵ Ibid.

³ Ibid.

⁶ Ibid.

for obviously if tetanus toxin is conducted by the axis-cylinders only antitoxin can be of little value, while if the lymphatics carry it vigorous antitoxin therapy is indicated.

The work of Meyer and Ransome⁷ seems to show that the conduction is entirely through the axis-cylinders. They showed that if tetanus toxin were injected subcutaneously in an extremity, and after some time the nerve of this extremity were removed and the extract injected into another animal, it would develop tetanus. However, Teale and Embleton⁸ proved by reinjection experiments that after the injection of toxin in an extremity, within a short time, it is present in the blood, liver, spleen, etc., and even in the nerve of the opposite extremity, results which would be impossible if the toxin were conducted entirely by the axis-cylinders. In the same research it was demonstrated that blocking the neural and perineural lymph channels by the injection of iodine or colloids delayed the spread of toxin up the nerve. Furthermore, the experiments of Orr and Rous, confirmed by Teale and Embleton, showed that bacteria can travel along the neutral lymphatic sheath, thus inferring that tetanus toxin with its smaller molecule can do the same. Finally, Robertson⁹ injected the peripheral nerve paths with Richardson's blue and found the lymphatics of the motor nerves to be much larger than in the sensory, which would help to explain the more ready conduction of tetanus toxin by the motor nerve paths.

Thus the latest evidence seems to point to at least a partial conduction of toxin by the lymphatic route. As a basis for therapy it would be safest to take the position that Robertson assumes, namely, that tetanus toxin appears in the blood stream and other tissues and can be neutralized by antitoxin at any stage in its passage before its final and relatively undissociable union with the ganglion cells. Consequently, the greatest indication for treatment is to maintain as high a concentration as possible of antitoxin in the blood and lymph stream. This can most readily be done by large and frequently repeated injections, intravenously. The small series of cases reported here would confirm somewhat the efficacy and harmlessness of this method of treatment.

Summary. 1. Four cases of tetanus are reported which recovered after receiving large doses of antitoxin intravenously.

2. War statistics of tetanus treatment by antitoxin are difficult to interpret because of the effect of prophylaxis.

3. Experimental evidence shows that tetanus toxin is at least partly conducted by the perineural lymphatics.

4. Theoretically the maintenance of a high concentration of antitoxin in the blood and lymph is indicated in tetanus treatment.

5. Practically, this may be accomplished by large frequent intravenous injections.

⁷ Arch. Exp. Path. u. Pharm., 1903, xlix, 367.

⁸ Jour. Path. and Bact., 1919, I, 23.

⁹ AM. JOUR. MED. SC., 1916, clii, 31.

GONORRHEAL ENDOCARDITIS: REVIEW AND REPORT OF A CASE.

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It was seventeen years after Neisser had discovered the gonococcus and eleven years after Bumm had perfected the technic of demonstrating the organism before the gonococcus was proved to be the sole etiologic agent in a case of endocarditis. It had been observed several years before the discovery of the gonococcus that heart affections sometimes complicated gonorrhea. At this early date, when the etiology of gonorrhea was not known, the methods by which the complications were produced were in doubt except where *per continuum* explained the process. Bumm first contended that the gonorrheal process was limited to mucous membranes. Finger later asked the question if the secondary processes associated with gonorrhea were due to the gonococcus. He answers the question by saying that these processes may be (a) purely gonorrheal; (b) pyogenic organisms entering the body through the diseased mucous membrane or lodge at the areas which have been damaged by the gonococcus or the products of its growth; or (c) purely toxic.

In 1896 Thayer and Blumer reported a case of endocarditis which they proved was purely gonorrheal in nature. Thayer and Lazear reported another case in 1899. Since these reports a fair number of undoubted cases of purely gonorrheal endocarditis have been reported. Standard text-books on pathology and medicine have for a number of years given the gonococcus an important place in the list of organisms producing endocarditis.

The above-mentioned reports were the first to prove definitely that the gonococcus did not limit its affections to the mucous membranes. The percentage of cases of gonorrhea in which there is a septicemia is probably higher than is usually thought. It is not unlikely that the diplococcus in the blood will in a certain number of cases cause only transient symptoms, such as fever, chill and albuminuria; but in others, due to some abnormality in the local tissue or to some special property of the strain of gonococcus, there will develop metastatic lesions.

The process by which the gonococcus lodges on the heart valves and produces endocarditis is probably very similar to the process by which any other organism lodges there. A septicemia is essential. It is generally thought that the organisms lodge directly on the valves along the line of closure, this line of closure being just back of the free edge of the valve. The bacteria are thought by some to be mechanically caught along the line of closure. Rosenow has disputed the above and claims that the bacteria get to the valves

by way of the capillaries as emboli. However, it has been proved (Coen and von Langer) that capillaries do not extend out as far on the valve as the line of closure. A previously diseased valve is thought to play an important role in the developing of an endocarditis. The roughened or thickened valve or endocardium predisposes to the bacteria lodging and multiplying here.

It is an interesting fact that gonorrheal endocarditis occurs on the right side of the heart in about one-third of the cases. In the thirty-two cases of Thayer and Lazear, 32.2 per cent. had the lesion on the right side of the heart. The recent work of Wherry and Oliver offers a plausible explanation of this fact. They found that the gonococcus grew much more abundantly when the carbon dioxide tension was slightly increased at the expense of the oxygen tension. Thus the conditions in the right side of the heart would be more suitable for the growth of the gonococcus.

Gonorrheal endocarditis occurs more often in the male than in the female about two to one. It most often occurs in early adult life, that is, in the twenties. The time of its occurrence in reference to the primary infection is variable. Some cases have occurred a few days after onset of primary infections while others have occurred late in the attack in persons who have had gonorrhea many times before.

There are two varieties of gonorrheal endocarditis: first a benign type and second a malignant type.

There is not much known definitely about the pathology of the first type, since this type very rarely comes to autopsy. It is entirely possible, though, that the toxin from the gonococcus can cause valvular changes. This is a sclerotic process. There is included under the benign type those infective cases which cause only slight inflammation in the endothelium, and possibly at times small verrucose vegetations are formed. These make up a certain percentage of the cases which show generalized symptoms and signs following gonorrhea. In cases of this kind a murmur at some stage of the disease can often be demonstrated. A positive blood culture may be obtained, but this alone is not conclusive evidence of an endocarditis. It seems that in a number of reports on this subject too much emphasis is placed on finding the gonococcus in the blood. This benign type may resolve with little damage or may progress to second type.

The second, or malignant type, of gonorrheal endocarditis has been studied more thoroughly because these cases usually come to autopsy. It is the tendency of the gonococcus to cause this second type of endocarditis. McCallum says ". . . the gonococcus is likely to give rise to large vegetations, which grow rapidly and are found in a crumbly soft state. Occasionally they are so massive as practically to occlude the whole valvular orifice. . . . a hint as to the nature of the infection may be gained from its frequent

occurrence in the valves of the right side of the heart, and from the rapid destruction of the valves themselves, so that one frequently sees great thrombus masses flopping back and forth on the end of a thread of tissue, which is all that remains of the valve."

The thrombotic vegetation begins as a small verrucose vegetation composed of new connective tissues, some wandering cells, mostly polymorphonuclears and gonococci. Fibrin and other elements of blood are deposited on this. The valve leaflets may be almost entirely destroyed by ulceration. The mural endothelium, most often contiguous to the valve, is usually more or less involved. This is usually the verrucose type. Infected emboli are frequently set free in the blood and metastatic lesions are often produced.



FIG. 1.—Pulmonary valve. Note destruction of left leaflet and the large thrombus attached to right leaflet, A to B.

For data relating to history and clinical findings the case here reported is cited.

As to treatment nothing specific can be mentioned. The general principles involved in treating any case of endocarditis should be carried out. If a focus of infection, as prostatitis or abscess is present, these should be properly treated. Substances given intravenously, like colloidal silver, have not given sufficiently satisfactory results in endocarditis to be recommended. In the chronic or subacute cases gonorrheal vaccines may be advisable.

CASE REPORT. Medical, No. 4616 (University of Virginia Hospital), male, white, aged twenty-eight years, admitted December 24, 1917.

Complaint. "Abscess in the liver."

History. (Summary).

Family History. Good.

Past History. Unimportant.

Present Illness. The patient passed the medical examination for the army in August, 1917. For some time before this he had complained of weakness, loss of appetite and pain in the stomach, after eating. In August he had urethritis (definite date not given) with no urologic complications. About the middle of September, 1917, began to have chills, these usually occurring during the afternoon or at night. They lasted from one to three hours and were followed by fever and sweats. Quinin in whisky seemed to stop the chills but did not prevent their recurrence. This condition continued, with slight improvement, until December 1, 1917, when the patient attempted to go back to work. He was forced to quit work at the end of the third day on account of a general swelling of his body and shortness of breath. He was advised by his home physician to go to bed, which he did not do, but walked about his room until coming to the hospital. Four days before admission he was told that he had a liver abscess.

Physical Examination. Poorly nourished white man, about thirty years of age, in a bed, on backrest, dyspneic on slightest exertion. Does not answer questions readily but is conscious; has spells of hiccoughing lasting from a few to several minutes. Skin is pale and has a lemon tint. Conjunctivæ are pale and have slight yellow tinge. Routine examination of eyes, ears, nose, mouth and throat negative; face not swollen. Cervical, axillary and inguinal glands palpable. Moderate pitting on pressure about ankles. Left knee-joint shows a small amount of swelling, slight or no tenderness; patella not floating; some fluctuation on the side of the patella. Knee-jerks normal.

Chest is asymmetrical, due to bulging of the eighth, ninth and tenth ribs on the right side. Lungs are resonant throughout; a few moist rales at bases behind. On examination of the heart a forcible cardiac impulse is seen in the fifth interspace and extending outward as far as the nipple line; the apex-beat is felt in the fifth interspace outside the left midclavicular line; no thrills felt. Percussion reveals that dulness extends 1 cm. to the right of the right sternal border. On auscultation a double murmur is heard more forcibly in the third left interspace near the sternal border, also quite readily at the pulmonic area. The systolic murmur is heard faintly at the apex. Both are rather low pitched, and the systolic is harsh in quality. The rate is 84 per minute. About every eighth beat is dropped. Blood-pressure is $1\frac{2}{3}$ / $\frac{5}{3}$. The abdomen is not distended; no dulness in flanks. Liver dulness extends in anterior midclavicular line, 2 cm. below the costal margin; edge not palpable; some tenderness over the liver. Spleen not palpable.

Genitalia apparently normal; no sores; no urethral discharge.

Laboratory Findings. On admission the leukocyte count was 15,000. Smear negative for malaria. Later findings in blood were: Leukocyte count, 17,300; red count, 3,590,000; hemoglobin, 45 per cent. (Dare); differential shows polymorphonuclear leukocytes 95 per cent.; lymphocytes, 2.5 per cent.; large mononuclears, 2 per cent.; transitionals, 5 per cent.; eosinophiles, 0 per cent.; smears were again negative for malaria; reds show a slight degree of poikilocytosis and anisocytosis; blood cultures negative (5 c.c. blood in 50 c.c. of glucose broth). Urinalysis: 800 c.c.; amber; 1020; acid; 1 mm. ring albumin; sugar negative; hyaline; finely granular; coarsely granular; pus and epithelial casts; 10 to 15 pus cells to high power field; few reds; bile positive. Daily urinalysis showed about the same as the above.

For temperature, pulse and respiration see chart.

Impressions. Ulcerative and vegetative endocarditis, probably of aortic valve because of the relative infrequency of pulmonic endocarditis.

December 25. Patient's condition unchanged. Had severe chill, lasting fifteen minutes, followed by profuse perspiration. Treatment consists of rest in bed; water freely; liquid diet; ice-bag to pericardium; tincture digitalis (fat-free), Mxx t. i. d.; morphin sulphate as sedative.

December 28. Perspires freely; vomited after nourishment; general condition poor; physical findings unchanged.

December 29. Patient irrational.

January 5. Condition of patient has gradually become worse; hiccoughing at intervals; skin cold and moist; pulse weak and irregular; breathing labored; lungs filled with moist rales and patient is in a profound stupor. Heart findings are the same as above except that the heart dulness extends 3 cm. outside the left midclavicular line.

January 5, 5 P.M. Respiration ceased.

Autopsy Report (three hours after death).

Pathologist. Dr Harry T. Marshall.

Anatomical Diagnosis. Gonococcal endocarditis and septicemia; ulcerative and vegetative pulmonic endocarditis; ulcerative aortic endocarditis; mural endocarditis; milky patch over the epicardium. Old pleural adhesions near the right diaphragm; puckered scar at the apex of the right lung; infarcts in lungs; thrombi in branches of pulmonary artery. Fatty degeneration of the intima of the aorta. Acute papillary nephritis; cloudy changes in kidneys; anomaly of right kidney. Fatty liver. Accessory spleens. Adenoma and hypertrophy of thyroid.

Heart. Muscle is very soft and pale. A large milky patch over the upper anterior surface of the right ventricle. On section the muscle is soft, opaque and cloudy. Right ventricle is distinctly distended. Tricuspid clear. A fresh chicken-fat clot fills the right

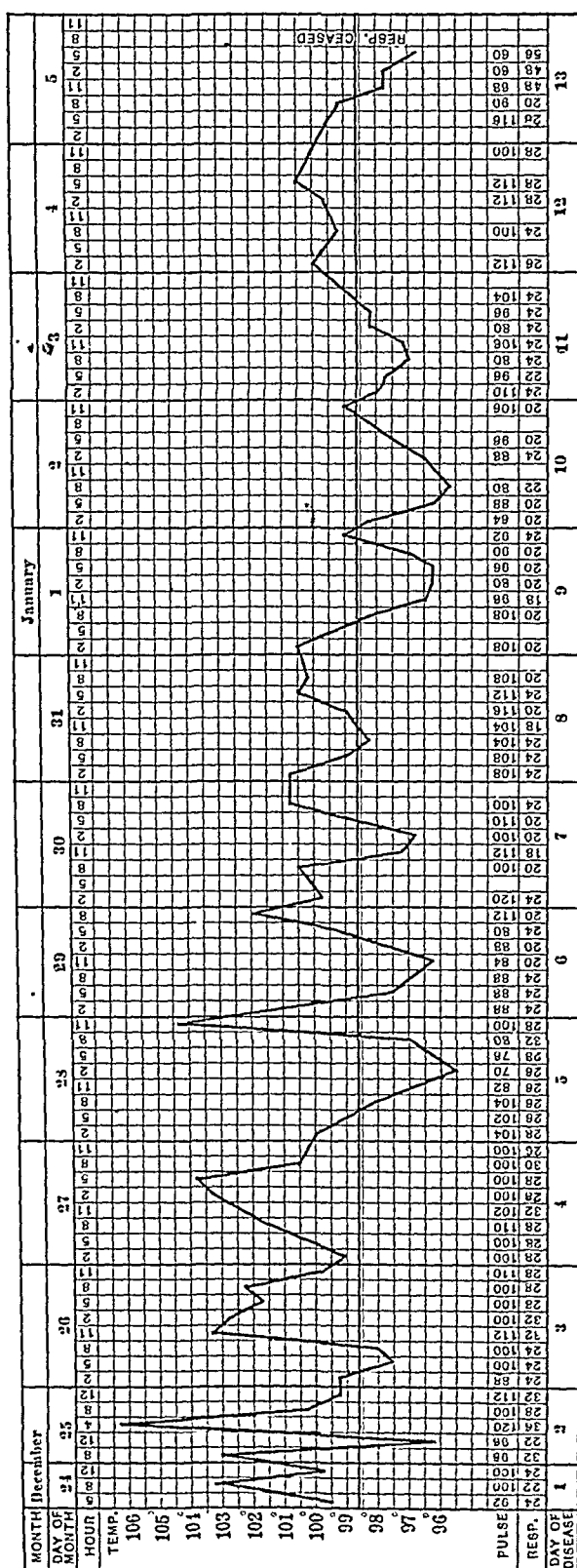


FIG. 2

ventricle and extends to the pulmonic valve, which also shows pronounced destruction from endocarditis. The left leaflet is almost completely eroded, only a few vegetations representing it. The right leaflet is buried in a thrombus, and this thrombus is cone shaped and furrowed in contour and extends at least three-quarters of an inch into the pulmonary artery; it is attached at its base to the valve leaflet. Below the valve small mural vegetations are covered with an elastic, recent clot continuous with the clot found in the right ventricle on the one hand, and with the valve thrombus on the other. Posterior leaflet of aortic valve shows a small ulceration and evidence of a slight chronic thickening. Otherwise the valves are clear except for a few verrucose vegetations on the aortic valve.

Smears from thrombi and heart's blood show Gram-negative, intracellular, biscuit-shaped diplococci.

Cultures from the heart's blood, and from thrombi negative.

The diagnosis in this case is based on a recent history of gonorrhea, negative cultures, morphology of organism in smears and the character of lesions found at autopsy. None of the above findings alone would be sufficient for making a diagnosis of gonorrheal endocarditis, but when taken together they prove beyond a doubt that the gonococcus is the etiologic factor.

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**EPIDEMIC ENCEPHALITIS: OBSERVATIONS ON A SERIES OF
FIVE CASES; AUTOPSY FINDINGS; PREDOMINATING
SYMPTOMATOLOGY; RELATION TO INFLUENZA;
PERSONAL CONCLUSIONS.**

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DURING the fall, winter and spring of 1918-1919, and again in 1919-1920, there have been reported from numerous sites in the United States a number of cases clinically known as epidemic encephalitis. The relative frequency of the disease is shown by the ever-increasing number of cases and case reports that are published in the medical literature. The earliest observations in this country were those of Peter Bassoe, Josephine Neal, F. A. Ely, B. Sachs, P. Wegeforth, J. B. Ayer and others, and since followed by those of F. Tilney and H. A. Riley, L. F. Barker and E. Cross and S. Irwin, etc. The predominating symptomatology, as reported by the above observers, has been markedly consistent, probably the best recognized of which are the lethargic state, the frequency of cranial nerve involvement, the spinal fluid findings and the relative frequency with which the disease is preceded by influenza. Our own experience with the disease dates from October, 1918 (Case I). Since that time we have had the opportunity of carefully studying four additional cases, the entire series of which follows:

CASE REPORTS These cases are from the Medical Wards of the Roosevelt Hospital, New York City, N. Y.

CASE I.—S. W., child, aged five years. Admitted October 24, 1918. Service of Dr. Rowland G. Freeman. Previous history of influenza.

History. Chief Complaint. Child is irrational and irritable; very restless.

Present Illness. About four days ago the patient, having just recovered from an attack of influenza and bronchopneumonia, was well enough to be up and play around the house. For two days the child appeared well and normal in her actions and was very bright and active. Two days ago there was a marked change in the child's disposition. She became irritable and then irrational, and within twelve hours was so much so that she did not recognize her grand-

mother. The patient was unable to articulate properly and did not seem to understand when spoken to. Did not complain of diplopia.

Past History. Usual childhood diseases; influenza. Otherwise always well.

Family History. Negative.

Physical Examination. Temperature, 102°; feeble pulse, 100; respirations, 24. Well-nourished child, restless, tossing about the bed; moderate opisthotonos. Rolling of the eyes. Face expressionless. Marked masked appearance.

Head. Moderate opisthotonos. Pupils equal, regular and react to light and accommodation. There is a marked nystagmus of both eyes in all directions; no strabismus; no ptosis; no diplopia. Fundi normal. Ears, nose and mouth negative except for enlarged tonsils.

Heart and Lungs. Negative.

Abdomen. Superficial reflexes exaggerated; otherwise negative.

Extremities. Knee-jerks equal but hyperactive (4 plus). Kernig, negative. No Babinski; no ankle-clonus. Romberg, 2 plus.

Laboratory Findings. *Urine:* Specific gravity, 1020; albumin, none; sugar, none. Few white blood cells and epithelial cells.

Blood. White blood cells, 22,000; polynuclears, 64 per cent.; lymphocytes, 36 per cent.; red blood cells, 4,500,000; hemoglobin, 80 per cent. Von Pirquet test, negative.

Spinal Fluid. Clear, normal pressure, eleven cells; 100 per cent. lymphocytes. Cultures, sterile. Smear, no organisms. Wassermann, negative. Globulin 1 plus. Colloidal gold curve, 1.2.2.1.1.1.1.2.0.0.

Course. Patient was intermittently stuporous and restless. Showed first sign of awakening mental activity on November 12, 1918, nineteen days after onset. From this time on mental condition became rapidly brighter. Child began to take nourishment and showed an interest in her surroundings. The normal facial expression reappeared and the nystagmus of the eyes was absent on November 15, 1918. The child was allowed out of bed on November 18, 1918, and it was then found that she had lost all power to use her lower extremities and could not walk or even stand up unassisted. This flaccid paraplegia of the lower extremities was very persistent, and there was also a marked diminution of the muscle strength of the left arm and hand. Even with returning muscular power the child seemed to have forgotten how to walk and had to be actually taught, first crawling about on hands and knees and then slowly toddling about like a child of one year. She was discharged absolutely cured, with normal use of all extremities on December 15, 1918.

CASE II.—K. H., housewife, aged thirty-nine years. Admitted February 5, 1920. Service of Dr. John S. Thacher. Previous history of influenza.

History. Present Illness. Patient admitted in condition of lethargy. Sent into the hospital with a diagnosis of meningitis, but showed none of the ordinary symptoms. Seemed to be in possession of all her mental faculties except that she took absolutely no interest in her environment. When engaged in conversation her replies were either "Yes" or "No" or some other monosyllable. She has been in this condition for fourteen days, more marked for the past seven days.

Past History. About one month ago the patient had influenza, which merged into this condition. At the onset of the attack she had severe headaches, mostly frontal, at times occipital; sore-throat and pains in the back. Her temperature was 101° F. Her pulse was never above 80. Twitching of the hands and face, mostly on the left side. Transient systolic heart murmur at base. Patient was never in this condition before.

Family History. Negative; married; children all healthy; nothing like this in family before.

Physical Examination. Temperature, 102° F.; respiration, 20; pulse, 80. A rather large, fleshy, but not obese woman, resting quietly in bed, breathing quietly and regularly. Patient conscious but takes absolutely no interest in her surroundings. Said to be slightly disoriented but not apparent on admission. There is no marked blankness to the facial expression.

Head. Pupils small, moderately contracted, but react to light and accommodation. Marked ptosis of the left lid and slight ptosis of the right lid. Eye movements not coördinated. Right eye shows moderate external strabismus. Disks do not stand out sharply, less white than usual, but not definitely abnormal. No nystagmus.

Neck. No glands. Thyroid, negative.

Chest. Breasts negative. Lungs, clear. Heart, negative. Slight systolic murmur at apex.

Abdomen. Liver and spleen not palpable. Superficial abdominal reflexes present and of normal intensity.

Extremities. Muscle strength essentially normal. Left knee-jerk more active than right. No Babinski or modifications. No Brudzinski. Slight suggestion of a Kernig.

Laboratory Findings. Urine: Negative throughout. Temperature on admission, 102° F. First week between 99° and 101° F.; second week between 98° and 100° F.

Blood. White blood cells, 12,200; polynuclears, 76 per cent.; lymphocytes, 24 per cent.; culture, sterile; Wassermann, negative; blood-pressure, 98/72. Widal, negative.

Blood Chemistry. N. P. N., 32.90; urea nitrogen, 15.9; uric acid, 2.10; creatinin, 0.91; sugar, 0.09.

Phenolsulphonephthalein Test. 60 per cent. dye elimination in two hours.

First Spinal Fluid Examination. February 6, 1920. Clear, normal pressure. Eighty-one cells per cubic millimeter; 100 per cent. mononuclears. Culture, sterile. Smear, no organisms. Wassermann, negative. Globulin, 1 plus. Colloidal gold curve, 0.0.0.1.1.2.1.0.0.

Second Spinal Fluid Examination. March 2, 1920. Clear, normal pressure. Eight cells per cubic millimeter; 100 per cent. mononuclears. Wassermann, negative. Culture, sterile. Smear, no organisms. Globulin, 1 plus. Colloidal gold curve, negative.

Course.

February 5. Semicomatose all day.

9. Condition unchanged.

11. Slightly irrational. Ptosis of lids were marked.

14. Not so lethargic—awake for several hours.

16. Markedly brighter mentally.

29. Patient continues to improve. Facial expression has returned. Begins to show conversational interest in her surroundings. Ptosis of eyelids less marked. External strabismus of right eye now gone.

March 5. Mentality normal. Ptosis of right lid gone. Ptosis of left lid much less marked. Facial expression animated and bright.

6. Discharged cured.

CASE III.—E. L. G., child. Service of Dr. Rowland G. Freeman. No previous history of influenza.

History. Chief Complaint. Diplopia, headache, frontal and occipital, dizziness, duration twelve days.

Present Illness. Nineteen days ago patient started to complain occasionally of being dizzy and having pains in the head. His father noticed his eyes did not "look quite right," and once or twice, when walking, he stumbled into objects, furniture, etc. In the morning, while apparently well and getting ready for school, he told his father he had two neckties on. This was the first time they had noticed any diplopia. For the next seven days, slowly but progressively, the child became mentally duller. At first it was hardly noticeable, except to his parents. Ten days ago he went to school for the last time. He left home in good spirits and returned from school as though walking in a trance. He was put to bed at once and a physician was called. He was pale, breathing quietly, and his pupils were dilated. At this time the child could not be aroused. The next morning he was awake and considerably brighter, but still very listless. He has been better at times, but up until the day of his admission to the hospital he was always lethargic. Occasionally he would rouse and speak with intelligence and take an interest in his surroundings. On two occasions, one night and five nights

before admission, he twitched as he lay in his stupor. This twitching was confined chiefly to the left side. The face and hands were chiefly involved. In the morning of the day of his arrival at the hospital he was fairly bright, took an interest in his family, the snow storm and the automobile ambulance. Soon after admission he sank into a stupor and remained that way. He could be aroused, but would not reply to questions. From the day of his return from school the child has taken only liquid food. He is unable, apparently from lack of desire, to chew even the smallest pieces of food. In his markedly depressed periods he will not rouse or take food or water.

Past History. Tonsillitis one year ago. Appendicular colic at times. Has had measles, whooping-cough and chicken-pox.

Family History. Father and mother living and well. One brother living and well. No history of fainting spells in the family. No tuberculosis, cardiorespiratory or chronic disease in the family.

Physical Examination. Temperature, 99.6° F.; pulse, 100; respirations, 24.

General. A thin but well-developed lad of nine years, resting quietly in bed. Takes no interest in his surroundings. Does not speak when spoken to except in monosyllables. There is a blank facial expression.

Head. Any sudden bright light will cause him to turn his eyes away but not his head. Teeth good. Tongue coated. Pharynx hard to see because of lack of coöperation, but apparently negative. Eyes: Pupils moderately contracted, equal, react to light and accommodation. Fundi negative. Movements are not coördinated. Slight external strabismus of right eye. No nystagmus.

Neck. Slightly stiff (of muscular and not meningeal origin). When the head is flexed it maintains position until muscular fatigue causes it to drop back on the pillow gradually.

Chest. Heart and lungs negative.

Abdomen. Superficial abdominal reflexes present but not exaggerated. Liver and spleen normal.

Extremities. When placed in one position they remain there until muscular fatigue lowers them (catatonia). Back stiff (muscular resistance). Brudzinski sign present. Babinski suggestive in left foot but not in right. Knee-jerks present and equal. Reinforced Babinski negative. Bilateral Kernig positive.

Laboratory Findings. *Urine:* Straw-colored; acid reaction; specific gravity, 1020; no albumin; no sugar; no red blood cells; a few white blood cells. Acetone and diacetic absent. Throughout sickness it varied but little from this.

Blood. Pressure 112/70. White blood cells, 10,200; polynuclears, 74 per cent.; lymphocytes, 26 per cent.; Widal (—). Throat culture, negative. Schick test, negative. Von Pirquet, negative; Wassermann, negative.

First Spinal Fluid Examination. Day of admission. Clear, normal pressure; 43 cells, 96 per cent. mononuclears. Cultures, negative. Smear, no organisms. Spinal fluid Wassermann, negative. Globulin, 1 plus. Colloidal gold curve, 0.0.1.1.2.0.0.1.0.

Course. Patient continued in his lethargic condition for seven days. Would rouse and speak in monosyllables when shaken. The blank facial expression was marked. Muscular rigidity of left arm and leg persisted. On the eighth day after admission patient began to show an interest in his surroundings. There was a gradual diminution in the lethargy. On the fourteenth day the spasticity of the left arm and leg was gone and there was a marked improvement in the facial expression. Patient was discharged on the twentieth day entirely well. A second spinal fluid examination on the tenth day gave the same findings as the first one.

CASE IV.—E. F., male, aged forty-two years. Admitted February 12, 1920. Service of Dr. Evan Evans. History of influenza.

History. Chief Complaint. "Nervousness." Sudden onset. One week's duration.

Present Illness. Two weeks ago the patient developed influenza. This cleared up in about one week. Patient then gradually became exceedingly "nervous," and this condition has grown progressively worse. There has been also a general feeling of malaise and drowsiness for the past three days. No diplopia. No subjective ataxia. No headache. Appetite poor. Bowels regular.

Past History. No previous illness. Chancre and gonorrhea denied.

Family History. Negative.

Physical Examination. Temperature, 98.8° F., pulse, 90; respirations, 24.

Head. Eyes, pupils equal, regular and react to light and accommodation. No strabismus. No ptosis. No nystagmus. No diplopia. Nose, ears and mouth negative. Fundi negative.

Neck. Negative.

Thorax. There is a marked myotatic irritability of the somatic muscles of the arms and thorax.

Heart and Lungs. Negative.

Abdomen. Liver and spleen not palpable. No masses; no tenderness. Superficial abdominal reflexes greatly increased; marked myotatic irritability and lateral to-and-fro twitchings of the abdominal muscles.

Extremities. Knee-jerks equal but hyperactive (4 plus). Romberg test, markedly positive. Kernig test, negative. Brudzinski, negative. No ankle-clonus. No Kernig.

Positive Findings on Admissions. Ataxia of both legs. Myotatic irritability of muscles of arms, thorax and abdomen and to-and-fro twitchings of abdominal muscles. Drowsiness,

Laboratory Findings. Urine: Acid, 1028; albumin, a trace; no sugar; few white blood cells.

Blood. White blood cells, 8200; polynuclears, 78 per cent.; lymphocytes, 22 per cent.; hemoglobin, 85 per cent.; red blood cells, 4,800,000. Wassermann, negative. Pressure, 140/90.

First Spinal Fluid Examination. February 14, 1920. Clear, normal pressure. Seven cells, 100 per cent. mononuclears. Culture, sterile. Smear, no organisms. Wassermann, negative. Globulin, 1 plus. Colloidal gold curve, 1.2.2.4.4.4.3.3.0.

Second Spinal Fluid Examination. February 25, 1920. Clear, normal pressure. Seven cells, 100 per cent. mononuclears. Culture, sterile. Smear, no organisms. Wassermann, negative. Globulin, 1 plus. Colloidal gold curve, 5.5.4.3.3.3.3.2.0.

Blood Chemistry. N. P. N., 32.50; urea nitrogen, 15; uric acid, 1.8; creatinin, 0.9; sugar, 0.11; carbon dioxide, 50.

Course. February 25, 1920. From the time of admission the patient became very listless and drowsy, with sudden irrational outbursts. The speech, which was quite coherent on admission, is scarcely intelligible, and is jerky and mumbled. Patient more stupid.

Eyes. Pupils unequal. Right larger than the left. Both react to light. Tongue deviates to the left; marked tremor of eyelids, lips, muscles of expression and hands upon executing any movements of these.

Neck. Somewhat stiff.

Heart and Lungs. Still negative. Myotatic irritability, 4 plus. Reflexes of upper extremities, 3 plus. Reflexes of lower extremities, 3 plus. Babinski, negative. No clonus.

These findings persisted unchanged. There was a noticeable absence of the "mask face" appearance, found in all of the other cases. The lethargic element was markedly present and remained until the death of the patient on March 3, 1920.

Autopsy Findings. Postmortem of E. F., aged forty-two years. Died March 3, 1920.

Autopsy, March 4.

Autopsy performed by Dr. Rolfe Floyd at Roosevelt Hospital.

Clinical Diagnosis (Medical Division): Encephalitis lethargica.

Anatomic Diagnosis. No cause of death in gross.

Chronic nephritis (slight).

Edema and congestion of lungs.

Old pulmonary scar.

External Examination. Body of an adult, white, male, very emaciated; rigor mortis moderately developed. No edema; superficial nodes not felt. Eyes, ears and nose normal. External genitals normal. No evidence of status lymphaticus except a wide pelvis. Subcutaneous fat much reduced and very yellow. Muscles very red; all tissues dry; blood volume small.

Internal Examination. Peritoneal cavity is normal.

Vault of diaphragm is at fourth space, right and left.

The right pleural cavity contains no fluid. There are some moderately firm adhesions over the upper lobe.

The left pleural cavity is normal.

The right lung shows some congestion and edema and a few hemorrhagic spots in the lower lobe, which resemble agonal hemorrhages; no gross consolidation; a very little purulent bronchitis of the small tubes.

The left lung shows the same condition, but there is, in addition, a puckered scar in the upper part of the left lower lobe, and about this the bronchi contains more pus of foul odor.

The large bronchi of both lungs are moderately congested and coated with a little mucopus; the hilus nodes are normal, no old tuberculous foci being found in them.

The larynx and trachea are normal.

The thyroid gland is normal, the thymus not recognizable.

The pericardium is normal except for a hemorrhagic spot under the visceral layer, about 5 cm. in diameter.

Heart is normal in size, valves, walls and coronaries.

Tongue, pharynx and esophagus normal.

Stomach mucosa shows an acute, patchy congestion of only moderate grade.

Small gut shows marked congestion of the upper jejunum, otherwise normal.

Large gut normal except for a small pin-head ulcer in the sigmoid. The rectum contains a large mass of soft feces, perhaps a pint, while the rest of the large gut is comparatively empty.

Nodes of mesentery are large, white and flat, the largest being 1 cm. across.

Liver normal, weighs 1500 grams.

Gall-bladder normal.

Spleen normal, weighs 180 grams. Follicles can be seen.

Pancreas normal.

Suprarenals normal.

Kidney very dark red, smooth, with a decidedly adherent capsule. On section the dark color is very evident but the markings are pretty good and the glomeruli can be seen. In one kidney there is a whitish nodule 2 mm. across in the cortex which looks like a fibroma.

Pelvis, ureters, bladder and prostate normal.

Pia is a little congested and looks a little dry. There is a slight adhesion to the dura over the tip of the left temporosphenoidal lobe.

Cortex normal except for a slight area, about 1 cm., across which is soft and yellow over the outer aspect of the right temporal lobe.

Centrum orale normal.

Ventricles, ependyma and choroid plexus normal.

Basal ganglia normal except that the vessels paths can be traced as white grooves after wiping the cut surface with knife. At the back of the left thalamus the vessels after section show like small dark pits, but this appearance cannot be called hemorrhagic.

The cerebellum, pons and medulla are normal.

Cerebral arteries normal.

Pituitary normal.

Ethmoid, frontal and sphenoid sinuses normal.

Middle ears normal.

Venous sinuses of dura normal.

MICROSCOPIC LESIONS OF E. F.

Lung 1. Congestion, edema and bronchopneumonia. The ordinary picture of edema and congestion, and is associated with peribronchitic zones of pneumonia which vary much in size and in which the chief component of the exudate is pus. A secondary bronchopneumonia.

Lung 2. Similar to "1," but the pneumonia is insignificant and there are areas in which the spaces are filled with blood; very likely agonal.

Lung 3. Interstitial pneumonia; from the scarred region. There is much fibrous tissue, with congested vessels and one area of hemorrhage. The wall of a damaged bronchus, probably dilated, is made of vascular granulation tissue which completely replaces all the layers of the normal wall. Some remnants of the epithelium are left. There is nothing in the section to mark the original process as tubercular, and it may well be the result of a long postbronchopneumonia.

Tongue. Circumvallate papillæ normal.

Liver. Slight acute congestion, somewhat patchy in distribution.

Spleen. Normal.

Pancreas. Normal. Islands hard to find.

Kidney 1, 2, and 3. Acute congestion, moderate. No connective tissue anywhere to explain the adherent capsule.

Thyroid. Normal.

Mesenteric Nodes. Normal. Rather too many long connective-tissue nuclei in the sinuses and one follicle shows a lighter center with big endothelial cells in it.

Retroperitoneal Node. Chronic adenitis. There is a definite inflammatory growth of connective cells and fibrillated ground substance in the lymph sinuses. The vessels are overful of blood.

Cortex and Pia 1. Normal. From vertex normal except for rather an excess of cells on the pial surface. These are not evenly distributed and are not seen in the meshes of the arachnoid. There is no perivascular exudate in the cortex.

Cortex and Pia 2. Cortical softening. From yellow softened area. There is a pathologic expression in the line of the cortex into

which the arachnoid dips. The cortex in this region shows an uneven margin, looser neuroglia than normal and a complete absence of pyramidal cells. In the overlying arachnoid are many elongated connective-tissue cells filled with yellow pigment.

Centrum Ovale. Encephalitis. A distinct round-cell infiltration along one vessel. Some light purple homogeneous rounded masses are scattered about. Significance unknown.

Left Optic Thalamus. Encephalitis. An extremely marked lesion showing massive perivascular round-cell exudate about many vessels. Few round cells lie even along the capillaries. Some vessels show none, some very few. Others seem to be nearly obliterated by the massive exudate. Often the exudate encircles both artery and vein running side by side. Sometimes some red cells lie outside the vessel walls among the round cells; in one instance only is there a very minute hemorrhage which goes beyond the perivascular lymph space. There are many globules of hyalin light purple substance, sometimes scattered along a diseased vessel. They may be brain sand. There seems to be an excess of round cells all through the tissue, but this is difficult to determine. The inflammatory cells run strictly true to type, no polynuclears being seen.

Right Thalamus. Encephalitis. Same lesion as shown above, perhaps not quite so pronounced.

Left Caudate Nucleus. Normal. Some vessels show a few too many cells in their outer coat, but without the lesion found elsewhere these would be passed as incidental and without pathologic significance. The ependyma is normal.

Right Caudate Nucleus. The perivascular infiltration, though much less than in the thalami, is distinct and characteristic.

CASE V.—E. M., male, aged twenty-three years. Admitted May 26, 1920. Service of Dr. A. E. Sumner. No previous history of influenza.

History. Chief Complaint. Sleepiness. Headache. Diplopia. Onset gradual. Duration three weeks.

Present Illness. About three weeks ago patient had an occipital headache and also some indefinite pain in the epigastrium. This disappeared, but the headache returned and has remained constant. Two weeks ago the patient began to have difficulty in vision, could not read letters and could not see objects distinctly, held near to him. He then noticed that an object would appear double to him, *i. e.*, diplopia, and this symptom has persisted. He has been very sleepy since the onset, so much so that he can sleep for twenty-four hours in succession without any desire to awake. There has been no stiffness of the neck, no vomiting, no cardiac or respiratory symptoms.

Past History. No previous illness. No history of influenza or pneumonia. Chancre one year ago; gonorrhea denied.

Family History. Negative.

Physical Examination. Temperature, 99.6°; pulse. 80; respirations, 20. Patient lying quietly in bed and apparently in a sound sleep.

Head. Marked absence of normal facial expression and appearance of the so-called "mask face."

Eyes. Both pupils irregular, react sluggishly to light, but normal to accommodation. There is a fine lateral nystagmus of both eyes. Spasm of right eyelid and suggestion of ptosis. Marked diplopia. No strabismus. Fundi, normal.

Nose, Ears and Mouth. Negative.

Neck. No stiffness; no masses.

Thorax. Lungs. Negative.

Heart. Negative.

Abdomen. Spleen and liver not palpable. No masses; no tenderness. Superficial abdominal reflexes normal.

Extremities. Knee-jerks very sluggish but equal. No Babinski. No ankle clonus. Brudzinski sign absent. Romberg, negative. Kernig, negative.

Laboratory Findings. Urine: Acid; 1032. No albumin. No sugar. Occasional white blood cells.

Blood. White blood cells, 8400; polynuclears, 77 per cent.; lymphocytes, 23 per cent.; red blood cells, 4,800,000; hemoglobin, 88 per cent.; Wassermann, negative.

First Spinal Fluid. May 26, 1920. Clear; normal pressure; forty-three cells; 100 per cent. mononuclears. Spinal fluid Wassermann, negative. Globulin, 1 plus. Culture, sterile. Smear, no organisms. Colloidal gold curve, 1.1.3.3.3.2.1.0.0.

Second Spinal Fluid. May 28, 1920. Findings same as in first lumbar puncture except that thirty-six cells, 100 per cent. mononuclears. Colloidal gold curve, 1.1.3.4.4.3.2.1.0.

Third Spinal Fluid. June 2, 1920. Findings same as first and second lumbar punctures except that nineteen cells, 100 per cent. mononuclears. Colloidal gold curve, 0.1.1.3.3.3.2.1.0.

Blood Chemistry. N. P. N., 35.6; urea nitrogen, 16; uric acid, 1.9; creatinin, 0.9; blood sugar, 0.13.

Course. The patient ran an uneventful course. He continued lethargic, with the above physical findings until June 3, 1920. From this time on the lethargy gradually disappeared and on June 7, 1920, patient was out of bed. The diplopia disappeared by June 5 and by June 10 the pupils reacted normally to light, but continued to be somewhat irregular. Facial expression rapidly became normal. The patient was discharged cured on June 14, in normal health.

DISCUSSION.

The Clinical Picture. The picture given here is a composite one and is intended to show the majority of the clinical findings, all of which do not occur in any one given case.

The onset in the majority of cases is insidious. At times, however, the onset may be sudden, with rapid development of the symptoms, as in Case I, and a marked tendency to irritability and restlessness rather than an initial lethargy. The temperature is usually normal, with a normal pulse and respiration ratio. Rarely, though at times, a sore-throat is noticed, as in Case II; more commonly diplopia, headache, either frontal or occipital, with a marked feeling of sleepiness, is complained of. In early cases these symptoms tend to make one think of a beginning meningitis, typhoid or poliomyelitis, but there is usually no trouble in ruling these out either on clinical grounds or laboratory findings within a few days. By far the commonest and most predominating symptoms at the onset have been the persistent feeling of malaise and sleepiness, from which the disease has taken its name. The next most common subjective symptom in our experience has been the diplopia.

As the disease progresses it has been a fairly constant finding to have some cranial nerve involvement. The commonest abnormality in this respect is to be seen in the eyes. Irregularity of the pupils, with sluggish reaction to the light, was seen in 1 case, ptosis of one or both lids in 2 cases, nystagmus in 2 cases, diplopia in 2 cases, strabismus of one or both eyes in 2 cases; the fundi, however, never have shown pathologic changes in our experience. There is one sign that we found in 4 of our cases and which does not seem to be discussed much in the literature. That is the marked absence of all facial expression, an ironing out of the facial lines, which gives them an appearance that is nearly typical of the "mask face" of paralysis agitans. This sign is persistent throughout the course of the disease, but seems to disappear with the loss of the lethargy and a return to normal mental activity. The patient's absolute loss of interest in his environment is portrayed extremely well in the facial appearance that he presents to the examiner. From the above findings it would seem that the oculomotor, trochlear, abducens and facial nerves are the ones most frequently affected, and that apparently the olfactory, auditory and optic nerves are never involved. The remaining physical findings vary and seem inconstant. Exaggeration of the superficial abdominal reflexes was observed in 2 cases and was present to normal degree in the remaining 3 cases. Brudzinski's sign was obtained in 1 case. In Case IV we found marked myotatic irritability of the muscles of the abdomen, thorax and upper extremities, and there was also present continuous spasmodic contractions of the entire abdominal muscle group. This lateral twitching was constant and persistent in this case, but was not found in any of the other cases.

In considering the laboratory findings as a part of the clinical picture we find that they are practically of no assistance, except where we consider the spinal fluid. Here, however, the findings are fairly characteristic and often are the deciding factor in arriving

at a definite diagnosis. The spinal fluid was always clear and the pressure was not increased. The cell count, however, was above normal and varied from seven cells per cubic millimeter to eighty-one cells per cubic millimeter, and were practically 100 per cent. mononuclear leukocytes. The cell count seemed to return to normal as the disease diminished in intensity. Globulin was present in every case. The Wassermann reaction was negative in every case. Smears and cultures were consistently negative. The colloidal gold curve, however, proved to be of interest in several cases. In Case IV the curve was tabetic in type in the first spinal fluid. The curve done on the second spinal fluid, drawn off eleven days later, was, however, paretic in type. In Case V the curve was tabetic in type on three separate occasions and the fluid was obtained at intervals of two and five days respectively. In the remaining cases the colloidal gold curve was negative. It would seem that the gold curve findings are variable and not consistent. Thus in Case III¹ of the series of Barker, Cross and Irwin the curve was on one occasion a "combined paretic and meningitic curve" and on another occasion was "leutic in type." The finding of either a luetic or paretic type curve, however, in a patient whose spinal fluid Wassermann is negative and whose clinical symptoms point to encephalitis should be of significant value.

The clinical course is usually typical. The patient remains in a lethargic state for a variable length of time and then spontaneously begins to wake up and gradually return to normal mental activity. At this time the cranial nerve findings diminish in intensity and disappear and the spinal fluid findings return to normal. Sequelæ are rare. In only 1 case (Case I) did we observe any marked after-effect, and in this case the flaccid paraplegia with the loss of the memory of how to walk rapidly passed away. Recovery is the usual terminal result, but in Case IV the patient died. This was the only mortality.

Etiology. The etiology at present is obscure to the last degree. It has been noticed, however, that in the majority of cases there is a preceding history of influenza, as in Case I, II, and IV of our series. This finding is not always constant, however, and what significance it may have on the ultimate etiology no one seems able to say. The smears and cultures taken from the spinal fluid are consistently negative and the absence of temperature, leukocytosis and other signs of sepsis tend to discredit the idea of the condition being an acute infection. The supposition of a filtrable virus is speculation at the best.

Pathology. The pathologic findings are well summarized in the autopsy report of Case IV. The gross anatomic findings showed

¹ Encephalitis, Lewellys F. Barker, M.D., Ernest S. Cross, M.D., and Stewart S. Irwin, M.D., Baltimore, Md., AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 1920, clix, 170.

no apparent cause of death, there being observed only a chronic nephritis, edema and congestion of the lungs and an old pulmonary scar. Microscopic examination of the brain, however, proved illuminating. Sections taken from the centrum ovale, the right thalamus and right caudate nucleus showed a distinct massive perivascular infiltration which varied greatly with different vessels. There were also observed many globules of hyaline light purple substance, sometimes scattered along a diseased vessel, and Dr. Rolfe Floyd suggested that they might be what is known as brain sand. The inflammatory cells ran strictly true to type, no polynuclears being seen. The sections taken from the cortex showed a cortical softening in one area, but were otherwise normal. The pathologic findings in this case correspond to those of other observers and show that the pathology is practically all of a microscopic nature.

SUMMARY OF SPINAL FLUID FINDINGS.

Character.	Cells.	Differential.	Smear.	Culture.	Wassermann.	Globulin.	Colloidal gold.
CASE I							
1. Normal pressure, clear	11	Lymphocytes, 100 per cent.; polynuclear, 0	No organisms	Sterile	Negative	+	1.2.2.1.1.1.2.0.0.
CASE II							
1. Normal pressure, clear	81	Lymphocytes, 100 per cent.; polynuclear, 0	No organisms	Sterile	Negative	+	0.0.0.1.1.2.1.0.0.
2. Normal pressure, clear	8	Lymphocytes, 100 per cent.; polynuclear, 0	No organisms	Sterile	Negative	+	0.0.1.1.1.0.0.0.0.
CASE III							
1. Normal pressure, clear	43	Lymphocytes, 96 per cent.; polynuclear, 4 per cent.	No organisms	Sterile	Negative	+	0.0.1.1.2.0.0.1.0.
2. Normal pressure, clear	40	Lymphocytes, 100 per cent.; polynuclear, 0	No organisms	Sterile	Negative	+	0.0.1.1.1.0.0.0.0.
CASE IV							
1. Normal pressure, clear	7	Lymphocytes, 100 per cent.; polynuclear, 0	No organisms	Sterile	Negative	+	1.2.2.4.4.4.3.3.0.
2. Normal pressure, clear	7	Lymphocytes, 100 per cent.; polynuclear, 0	No organisms	Sterile	Negative	+	5.5.4.3.3.3.3.2.0.
CASE V							
1. Normal pressure, clear	43	Lymphocytes, 100 per cent.; polynuclear, 0	No organisms	Sterile	Negative	+	1.1.3.3.3.2.1.0.0.
2. Normal pressure, clear	36	Lymphocytes, 100 per cent.; polynuclear, 0	No organisms	Sterile	Negative	+	1.1.3.4.4.3.2.1.0.
3. Normal pressure, clear	19	Lymphocytes, 100 per cent.; polynuclear, 0	No organisms	Sterile	Negative	+	0.1.1.3.3.3.2.1.0.

Conclusions. 1. Epidemic encephalitis in the majority of cases appears to be preceded by influenza.

2. The commonest clinical symptoms are the lethargy, the "mask face" and the diplopia.

3. The spinal fluid findings show an increase in the mononuclear leukocyte content, varying from normal to about one hundred cells

per cubic millimeter. The colloidal gold curve is variable, but in the presence of a negative spinal fluid Wassermann a tabetic or paretic gold curve in a patient with clinical symptoms of encephalitis should be of significance in the diagnosis.

4. The etiology is extremely obscure.

5. The pathology is characterized by perivascular infiltration of round cells in the nuclei of the bulb.

6. The majority of patients recover, but mortality does occur.

A REPORT OF AN EPIDEMIC WITH CERTAIN CASES PRESENTING THE PICTURE OF MENINGO-ENCEPHALITIS.

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OF lethargic encephalitis Achard¹ aptly says, "La maladie est polymorphe et acyclique." Clinically, epidemic encephalitis presents a most interesting group of syndromes which vary widely in their symptomatology. From time to time various forms of this disease have been added to the lethargic type, the first to be described. Syndromes resembling paralysis agitans, catalepsy, chorea, mania, bulbar palsy and other conditions are of such frequent occurrence that the name "epidemic encephalitis" has largely replaced the original term "lethargic encephalitis."

The lesions of this disease are fairly definitely limited to the brain-stem and the basal ganglia and consist of a perivascular infiltration of lymphocytes and plasma cells, engorgement of the vessels and degenerative changes in the ganglionic cells. The pathological changes, being most commonly confined to the brain-stem and basal ganglia, are sufficient to produce most, if not all, of the various syndromes described.

As a rule, however, the meninges have been relatively uninvolved by the pathologic process and examinations of the cerebrospinal fluid have seldom given a cell count that would indicate any marked degree of meningitis.

Hala and Smith² reported 1 case with definite signs of meningitis: The cell count in the cerebrospinal fluid was 480 cells per c.mm. and on the thirtieth day after the onset a motile, gram-negative bacillus

¹ Lethargic Encephalitis, Bull. de l'Acad. de méd., Paris, 1920, lxxxiii, 106.

² A Case of Meningo-encephalitis (Lethargic Encephalitis), Arch. Neurol. and Psych., 1920, iii, 160.

was found in smears from the spinal fluid. The pathological examination showed a purulent exudate in the sulci between the convolutions and a bacillus similar to the one in the spinal fluid was found present in the exudate. Laboratory animals died three to seven days after inoculation. The authors state that "the cultural characteristics of this organism on sugar coincide with those of no other organism which we know." Their conclusion is that "the bacillus probably belongs to some intermediate class of the colon-typhoid-enteritidis group."

Barker, Cross and Irwin³ stated that "only in a relatively few cases are the clinical signs of an outspoken meningeal irritation present. In one of our series there was pain in the neck and back, some rigidity of the neck, a positive Brudzinski sign and a positive Kernig sign. That there is a slight patchy involvement of the leptomeninges in the inflammatory process in many cases has been shown, however, by postmortem examinations and by the increased cell count and the positive globulin reactions in the cerebrospinal fluid."

Tilney and Riley⁴ found definite pathological changes in the spinal fluid in only 1 case out of 15. A diplostreptococcus was present in the fluid upon incubation, on culture, and in the stained smears. Subsequent tests of the fluid in the same case failed to show any organism to be present.

Bassoe and Hassin⁵ noted in one of their cases pial changes indicative of a mild leptomeningitis. The pia-arachnoid was infiltrated and frequently showed distended meshes containing congested hyperemic vessels.

Flexner⁶ reported increased cells and globulin in the cerebrospinal fluid but less than in poliomyelitis or meningitis.

Heiman⁷ states that there is frequently moderate rigidity of the neck. Of eight spinal fluids examined he found definite changes in only one, which had a cell count of 80 and a positive albumin test.

Bassoe⁸ suggests with some hesitation that this virus also may produce a syndrome characterized by meningeal irritation, and by irritation or paralysis referable to the spinal or cranial nerve roots. He reports 2 cases of this type.

* On the Epidemic of Acute and Subacute Non-suppurative Inflammations of the Nervous System Prevalent in the United States in 1918-1919; Encephalomyelitis; Polyneuritis and Meningo-encephalomyeloneuritis, *Am. Jour. Med. Sc.*, 1920, *clix*, 170.

⁴ Epidemic Encephalitis, *Neurol. Bull.*, 1919, *ii*, 106.

⁵ A Contribution to the Histopathology of Epidemic (Lethargic) Encephalitis, *Arch. Neurol. and Psych.*, 1919, *ii*, 24.

⁶ Histologic, Pathological and Clinical Facts and Epidemiology in Brief, *Jour. Am. Med. Assn.*, March 27, 1920, *lxxiv*, 865.

⁷ *Am. Ped. Soc. and Jour. Am. Med. Assn.*, July 19, 1919.

⁸ The Delirious and Meningoradicular Type of Epidemic Encephalitis, *Jour. Am. Med. Assn.*, 1920, *lxxiv*, 1009.

In a study of the literature with reference to the epidemiology of epidemic encephalitis, we found no reports of any definite contagiousness or of any tendency for the disease to spread through a household.

In the Local Government Board Report^a it is noted that of 58 cases investigated there was no instance of more than 1 case in the same household and Draper in this report says there was but one instance of more than 1 case in a family.

The following series of cases is of special interest because of the marked meningeal symptoms, the high degree of multiple incidence, the change in type of involvement and course and the bacteriological findings.

The epidemic occurred in a village of 743 people in southwestern Minnesota. There were 11 cases: 5 of which were in two related families; of the other 6 there were 3 in one family and 2 in another family. Six of the 11 patients died. Two of these patients were seen by one of us during their illness. Case No. IX was seen two weeks after the onset and case No. X was examined one week after the onset of the disease.

CASE I.—T. D., male, aged nineteen years, was the first possible case. He had not been in good health since 1916, when he was operated for exophthalmic goiter. His fellow workmen in the local produce company where he was employed had noticed an apparent failure in strength for several weeks before the onset of the acute symptoms.

On December 9, 1919, he came home from work complaining of not feeling well. The following morning he was nauseated and his chief symptom was fatigue. At 10.00 p.m., December 10, he became restless and delirious. A physician, who was called only shortly before death, noted some pulmonary involvement with blood tinged sputum and made a diagnosis of pneumonia. Death occurred at 3.00 a.m. December 11, about twenty-one hours after onset of symptoms.

CASE II.—M. G., male, aged twenty-five years, came to the village December 9 and left for home at noon, December 12. While in the village, he lived with his brother (Case VII) and his brother's wife (Case IX). This brother was the local butcher with a shop next door to the produce company where T. D. (Case I) worked. M. G. became ill on his way home on the train during the night of December 12-13. On the morning of December 13, he was driven from the station to his farm, became unconscious soon after his arrival home and died December 14 at 9.00 p.m. The entire dura-

^a Report of an Inquiry into an Obscure Disease, Encephalitis Lethargica, 1918. Reports of Local Government Board on Public Health and Medical Subjects, London, New Series No. 121,

tion of illness was about forty-eight hours. The diagnosis in this case was said to have been spotted fever.

CASE III.—J. R. (son of patient No. IV), male, aged ten years, became ill December 12 at 2.00 P.M. and died December 13 at 2.00 P.M. During his illness, he was not restless, but vomited a few hours after the onset of the illness and was delirious during the night. He did not seem to be in great pain or to suffer from distress. There was no Kernig or rigidity of the neck at any time.

CASE IV.—R. R. (mother of patient No. III), female, aged forty-one years, became ill December 13 with severe headache, mostly in the back of the head. The next morning, there was a purpuric rash on body and the temperature was 100.4° and the pulse 80. She got up, however, and walked about the room. On December 15 she complained of headache, backache, vomiting and pains in the limbs. At this time, she stated that she felt well except for the need of a good night's sleep. There was occasional deafness from the second day of illness. She felt drowsy most of the time but would answer questions rationally. There was a slight icteric tinge to the sclera. There was no Kernig or rigidity at any time. The leukocyte count of the blood was 34,300 per c.mm. Death occurred December 18 after a period of partial unconsciousness. The duration of the illness was about five days.

Autopsy was performed December 20, 1919, thirty-eight hours after death. The body was embalmed very shortly after death. The body was that of a well-developed stout woman. There was no edema; there was an icteric tinge to the scleræ of the eyes but this was not demonstrable on the skin. Small petechiæ were seen over the chest, abdomen, arms, hands and thighs. There were a few fresh fibrinous adhesions over the lateral and interlobar surfaces of the right lung. There was no pneumonia found. The spleen weighed 230 grams and showed the gross and microscopic evidences of acute splenitis. The liver showed fatty metamorphosis and chronic passive hyperemia. The kidneys showed moderate cloudy swelling both grossly and microscopically.

The brain showed a fairly large amount of greenish very thick purulent exudate in the pia-arachnoid over both cerebral hemispheres, especially in the sulci. This exudate was also found over the superior surface of the cerebellum. All the meningeal vessels were dilated, especially those on the left side. The lateral ventricles and the third ventricle contained no excess of fluid. Careful coronal sectioning of the brain showed no gross lesions in the brain substance. Smears of the meningeal exudate showed large numbers of polymorphonuclears and a moderate number of mononuclear leukocytes. There were a very few possible intracellular diplococci but one could not be absolutely certain about

these. No microscopic sections were made from the brain substance. The body had been embalmed so that cultural study was impossible.

CASE V.—H. K. (brother of patient No. VIII and nephew of patients Nos. VI and X and all lived in the same house), male, aged five years, became ill during the forenoon of December 18. He began to lie around during the afternoon but did not want to go to bed. In the evening when the father returned from work he noticed the boy looked very ill and called a physician, who made a diagnosis of epidemic cerebrospinal meningitis and gave 15 c.c. of serum intraspinaly. Patient did not complain of pain, and fever was not observed until shortly before death. There was a petechial rash scattered over the body. A spinal fluid examination from a puncture done on the evening of the 18th showed a very slightly cloudy fluid. The Nonne and cell count were negative and no organisms were found in smears or cultures (the spinal fluid examinations in these cases were made forty-eight to sixty hours after the spinal puncture, having been sent through the mail to Minneapolis). The patient died at 10.00 A.M., December 19, after an illness of only twenty-four hours.

Autopsy was performed December 20, 1919, twenty-nine hours after death. The body was that of a well-developed and well-nourished boy. There was no edema or jaundice. Scattered hemorrhages varying from the size of a pinhead to a diameter of 3 cm. were present in the skin of the trunk, limbs and face. Examination was permitted for the head only.

The meninges over the convex surface of the cerebrum showed moderate edema with a small amount of thick greenish purulent exudate in some of the sulci. There was a small amount of glairy semisolid material (not purulent) in the posterior horns of the lateral ventricles. Careful coronal sectioning of the brain showed no gross lesions within the brain substance. Smears of the meningeal exudate showed a predominance of polymorphonuclear leukocytes. Some cells showed what suggested intracellular gram-negative diplococci but in no instance were the organisms absolutely definitely demonstrated. Cultures from the meninges and lateral ventricles remained sterile.

Sections of the cortex extending for over 1 cm. into the cerebrum showed microscopically congestion of the vessels with perivascular lymphocytic infiltration. There was a proliferation of glial tissue and a diffuse lymphocytic infiltration. The neurone cells showed chromatolysis with invasion of lymphocytes (satellitosis and neuronophagia). These changes were found in the parts of the sections farthest from the surface of the brain.

The autopsies on this and the previous case were done on the same day. At that time it seemed probable to the pathologist

that he was dealing with cases of epidemic cerebrospinal meningitis; the first case had shown an abundant greenish thick purulent meningeal exudate with no sign of gross lesions in the brain substance. The smaller amount of the purulent meningeal exudate in the second case was thought to be due to the shorter duration of the illness, with death presumably in the stage of general bacteremia and just as the infection was beginning to localize in the meninges. Examinations of smears from the meningeal exudate were quite suggestive also. The encephalitis was proved only when the microscopic sections were examined. The lymphocytic character of the perivascular and diffuse infiltration; the depth to which the affection extended; the degree of the neuron cell changes all serve to differentiate this encephalitis from the shallow hemorrhagic encephalitis with polymorphonuclear leukocytic infiltration sometimes associated with the meningococcic meningitis.

CASE VI.—R. D. (sister of patient No. X and aunt of patients Nos. V and VIII and living with them), female, aged nine years, came home December 18 with stomachache and sat about the house during the day without expressing desires or complaining. Later there was headache, vomiting and general irritability. Serum treatment was started and continued through the illness. There was a positive Kernig the following day and the purpuric spots and herpes were present. Vision was lost in one eye on the 24th. Rigidity was noted as being less and hearing not so acute on December 25. Parotitis developed on the 29th. The attending physician considered the possibility of the condition being lethargic encephalitis. During the latter part of her illness she slept most of the time but her mind was clear when awake. The temperature went as high as 102° to 103° until January 2. Two spinal fluid examinations were made. December 20 the fluid was clear, Nonne and cell count negative and no organisms were present in smears or cultures. December 25: clear fluid, Nonne trace, cell count negative, no organisms in smears or cultures.

CASE VII.—J. G., male, aged twenty-nine years, living with patients Nos. II and IX and working next door to patient No. I, complained of general weakness on December 19. He had headaches, bowel disturbances and pain in the abdomen. No Kernig or rigidity was noted. He returned to work the following day and was considered as a possible abortive case.

CASE VIII.—M. K., female, aged thirteen years, living with patients Nos. V, VI and X, became ill about 11.00 A.M., December 21. On that date she complained of a mild headache and some pain in the back. The temperature was 102.5° and the pulse 120. She had a tendency to a positive Kernig and there was some pain

upon bending the neck. By the 24th she was apparently well. Spinal fluid examination on the 22d showed a clear fluid with a negative Nonne and normal cell count. No organisms were found in smears or cultures.

CASE IX.—C. G., female, aged twenty-five years, living with patients Nos. II and VII, began to have headache and vomited on December 24. There was some muscular rigidity after the third day and the Kernig sign was positive early in the course of the disease. Deafness developed on the 25th and blindness in the left eye on the 26th. There was general hyperesthesia from the onset of the illness. An erythematous eruption appeared on the 27th. She would talk rationally when someone was conversing with her but otherwise talked more or less irrationally. Headache was severe and persistent from the first. Hearing gradually returned and when last seen on January 11th, the patient was apparently slowly recovering. A spinal fluid examination made December 27th showed a slightly cloudy blood tinged fluid with a normal cell count and no organisms present in the smears. A Gram-positive organism was found in the broth cultures, but there was no growth on serum. On December 28 the fluid was cloudy, pus cells were present and staphylococci were found in smears and in broth and serum. The fluid examination on the 29th gave a cloudy fluid, flocculent. Pus cells were present but no organisms were found in smears or cultures.

CASE X.—R. D., male, aged twelve years, became ill on December 30. At the time of onset he was living with patients Nos. V, VI and VIII. His past history was negative except that he had had anterior poliomyelitis in 1916. His illness began with restlessness and pain in the distribution of the left supra-orbital nerve. On the 31st he complained of tenderness over the left eye. There was no rigidity or tremor. The pulse was 78 and the temperature 98.4°. On the second day of his illness there developed deep and rapid respiration with a respiratory rate of 40 to 60 a minute. There was occasional vomiting. The blood examination at this time showed a leukocyte blood count of 17,000. On January 1 he was able to walk to an automobile, go to another house nine miles away from the village, and walk upstairs to bed. The blood examination on January 4 gave a leukocyte count of 7600 and a red blood cell count of 4,000,000. On this date, there was some cough and expectoration, and percussion gave a higher pitched note over the right upper lobe. Temperature was 101° and the pulse 90. He became semidelirious on the 5th. He answered questions readily and there was no difficulty in his understanding what was said to him. His condition became worse on the seventh but there was no Kernig present and only slight rigidity on extreme

flexion of the neck. In the following few days the mild delirium continued. He would pick at imaginary objects in the air but

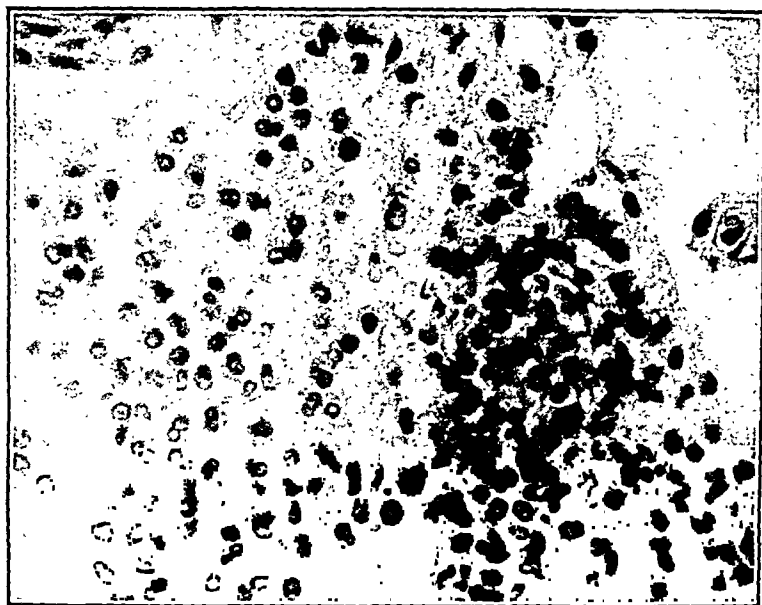


FIG. 1.—Case X. Meninges over cerebral cortex. Arachnoid infiltrated with polymorphonuclears, lymphocytes and endothelial leukocytes. Some extravascular red blood cells also shown.

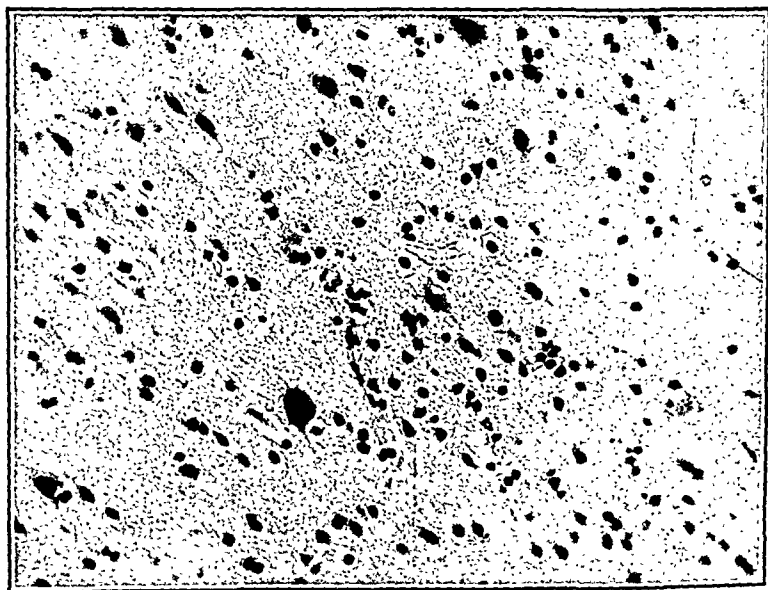


FIG. 2.—Case X. Subcortical white matter of cerebrum. Diffuse lymphocytic infiltration and glial proliferation.

memory and comprehension were unimpaired and in conversation he appeared normal. A neurological examination made on January 9 gave the following findings: Vision was subjectively fair; he saw objects larger or smaller at times. The fundi were normal



FIG. 3.—Case X. Midbrain. Perivascular lymphocytic infiltration.



FIG. 4.—Case X. Region of cortex. Satellitosis and chromatolysis of neurone cell.

except for a very slight edema of the disks. There was weakness of the right lateral rectus and a slight ptosis. The pupils were unequal but reacted normally to light and distance. There was



FIG. 5.—Case X. Region of cortex. Disintegration of neurone cell; also shows neuronophagia beginning.

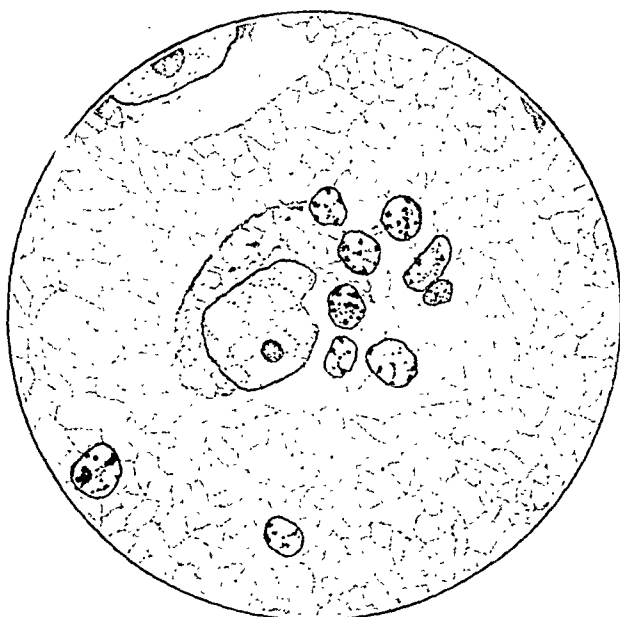


FIG. 6.—Case X. Basal ganglia. Advanced neuronophagia.

no diplopia; convergence was good. On looking to the right a very marked nystagmus was present. A twitching of the facial muscles was noted. Hearing was normal. Swallowing was unimpaired. The relatives thought that there was some change in his voice. He did not ordinarily complain of pain, but his sister said he complained of pain when bathed and of pain at times in the knees. Pressure over the extremities or stroking did not cause discomfort.

There was no atrophy present except in the left leg (poliomyelitis in 1916). General motor and psychic restlessness was evident. He constantly tossed about and had a coarse jerking of the arms and legs. In a general way this resembled choreic restlessness,

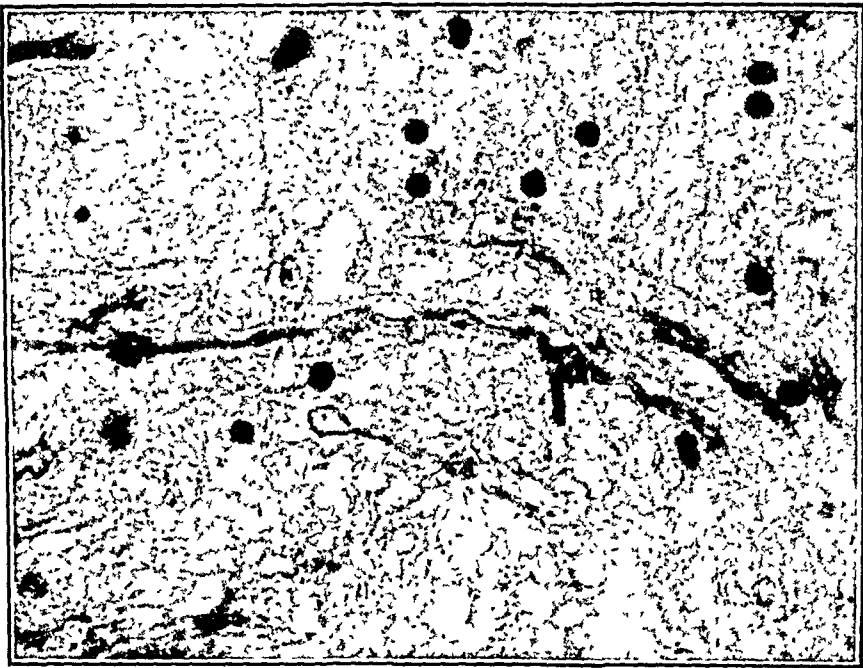


FIG. 7.—Case X. Internal capsule in region of thalamus. Myelin sheath degeneration; showing bulbous enlargements and irregular thickening of the sheaths.

but the movements were coarser and more purposeful although involuntary. A degree of ataxia was noted in the movements of the hands. The deep reflexes were all moderately active except in the left leg where the knee-jerk was absent and the ankle-jerk was much diminished. The plantar reflexes were both flexor in type and there was no ankle clonus. The abdominal reflexes were present. Memory and comprehension were good. He answered questions readily and intelligently. When not in conversation he sang and hummed to himself and also muttered some. He complained of feeling tired and drowsy and went to sleep at times while eating. Spinal fluid examination made January 8 showed a clear fluid, Nonne negative, normal cell count and no organisms

in the smears. Gram-positive staphylococci were present in the cultures. He died January 23, 1920, forty-one days after the onset of his illness.

At autopsy, January 25, 1920; thirty-three hours postmortem, the body was well developed and well nourished. There was no edema or jaundice and the pupils were regular and equal. The lips showed sordes. The serous cavities showed no adhesions and no excess fluid. On the anterior surface of the heart in the epicardium were about a dozen petechial hemorrhages, especially over the right ventricle. There were no other gross lesions in the heart aside from a slight hypertrophy of the left ventricles. The lungs showed no lesions aside from edema in the lower lobes. The spleen was enlarged and very soft and flabby. It showed acute splenitis both grossly and microscopically. The kidneys showed cloudy swelling. On the outer surface of the skull there were a few small hemorrhages. The upper surface of the cerebrum showed a considerable collection of serous fluid which was very slightly cloudy. On the inferior surface of the frontal and parietal lobes and over all the surface of the cerebellum, midbrain, pons, medulla and cervical portion of spinal cord there was congestion of the meningeal vessels with many small hemorrhages. Over these same areas there was a thick fibrinous exudate and in the sylvian fissure this exudate was fibrinopurulent in spots, causing obliteration of the fissure by adhesion. There was about 2.5 c.c. of clear fluid in each lateral ventricle. There was a small amount of thin serous exudate in both middle ears and mastoid cells. The mucous membranes of the middle ears were thickened. The frontal, ethmoid and sphenoid sinuses were normal.

On microscopic examination the various gross findings in the organs of the thorax and abdomen were corroborated. The brain, however, showed significant lesions. In the meninges there was a marked exudate in the subarachnoid space in addition to the edema and hemorrhages noted grossly. In the exudate medium-sized mononuclear leukocytes predominated. There were also numerous polymorphonuclear leukocytes and some lymphocytes. Brain substance: there was a perivascular lymphocytic infiltration, especially marked in the region of the basal nuclei and red nucleus, and somewhat in the cerebellum. Satellitosis, neuronophagia, chromatolysis and further neurone cell degenerations were found especially in the basal nuclei and pons. There was a very marked irregular swelling of the medullary nerve sheaths in the midbrain and pons with irregular thickenings of these sheaths. Small amounts of brown pigment were noted in some cells in the pons not far below the locus caeruleus. At least one clump of small bacilli was found in a stained section of the pons but no further bacteria could be demonstrated even in sections stained for both Gram-negative and

Gram-positive organisms. Cultures from the meninges, ventricles and brain substances were sterile.

Small bits of brain tissue removed from cortex, midbrain and pons, under aseptic precautions, were taken to the Division of Preventable Diseases of the State Board of Health and there inoculated intradurally into rabbits.

One rabbit died approximately forty-eight hours after inoculation. The other rabbits remained alive and apparently well. At autopsy the rabbit which died showed a very heavy fibrinous exudate over the lower lobe of the right lung and congestion of the organs, but no other gross lesions. A very small Gram-negative bacillus growing well on ordinary media was demonstrated in both pleura and heart's blood. This condition may possibly, though not necessarily, have been present before the inoculation. The microscopic examination of the brain was nevertheless significant and it seems entirely possible that the condition found there was related to the inoculation rather than to the pleuritis and bacteremia. In the meninges there was congestion with slight hemorrhage and rather slight diffuse exudate consisting principally of lymphocytes and plasma cells. The midbrain showed a marked perivascular infiltration of lymphocytes and diffuse lymphocytic infiltration and various degrees of degeneration of the large nerve cells with chromatolysis, satellitosis and neuronophagia. Perivascular lymphocytic infiltration was found also in the cerebrum and pons.

CASE XI.—After our last visit to the village, another case has developed in the family (X) and within six days after his death, and, therefore, related to patients Nos. VI, VII, VIII and X. This patient, T. K., aged fifteen years, is said to have had a typical lethargic type of encephalitis. The first symptom was noted January 29, 1920.

DISCUSSION. In these cases we have a rather remarkable sequence. The first cases (I, II and III) presented more or less the picture of an acute toxic condition without special localizing phenomena. In the next group (IV, V, VI, VIII and IX) the meningeal symptoms were prominent with, however, fairly definite evidence of an accompanying encephalitis. The last two cases (X and XI) were primarily encephalitis, with meningeal involvement occurring seven days after the onset of the symptoms in case No. X. In other words there was an infection of an extremely virulent type gradually becoming attenuated and presenting in this course three fairly distinct syndromes—an acute toxemia, a meningitis or meningo-encephalitis and an encephalitis.

In this connection it is interesting to note that in some of the previous epidemics botulism was suspected and a number of cases so diagnosed according to the report of the Local Government

Board (London). In the first cases of our series, botulism was thought of as a not unlikely diagnosis. The infection in these cases was so virulent and the course so acute that few localizing phenomena were present.

It seems likely that these cases are related etiologically to the hitherto reported cases of epidemic encephalitis. Two of these cases presented typical syndromes of "lethargic encephalitis," one of these (No. X) having the choreiform movements seen in a certain number of cases of epidemic encephalitis as well as the characteristic lethargy. In the history of case No. IV we note that the patient stated that she felt well except for the need of a good night's sleep. She was drowsy most of the time but would answer questions rationally.

The autopsies of cases Nos. V and X show lesions typical of epidemic encephalitis.

The perivascular lymphocytic infiltration, most marked in the region of the basal nuclei, the diffuse lymphocytic infiltration with glial proliferation, the degenerative changes in the nerve cells, the satellitosis and neuronophagia, have all been repeatedly described time and again in reports of epidemic encephalitis. The fact that these lesions may be found in the brain cortex, as in our case No. V, has previously been demonstrated in Bassoe's series of cases.

Pathologically, the distinctive feature in this series of cases is the extraordinary prominence of the meningitis. Although meningeal affection has been described by Bassoe and Hala and Smith we have seen no reports of cases showing such an extensive and marked involvement.

The acuteness of the disease process and the mortality of this epidemic are unusual. The mortality was 54.5 per cent. even when case No. VII is included (abortive case). Three of the 6 fatal cases died within approximately twenty-four hours of onset and one other died within forty-eight hours; one after five days and one after forty-one days. Epidemic encephalitis has hitherto been considered generally as a less acute disease with a fairly low mortality.

Besides the acuteness of the disease process and the marked meningeal involvement, these cases are notable for apparent contagiousness. There is a definite relationship between cases Nos. I, II, VII and IX; patients Nos. II, VII and IX lived in one house; patient No. I worked next door to patient No. VII. Patients Nos. III and IV lived in one house and became ill at almost the same time. Patients Nos. V, VI, VIII and X became ill while in the same house and within a period of eight days. During his illness patient No. X was taken to another house; within a short time after his death and in the house where he died, case XI developed the disease. All the 11 cases are included in these three

groups. The first 10 of the 11 cases developed within a period of thirteen days.

	Duration.	Outcome.	Date of onset.	Relationship.
I . . .	21 hours	Died	Dec. 9, 1919	a
II . . .	48 hours	"	Dec. 12, 1919	a
III . . .	24 hours	"	Dec. 12, 1919	b
IV . . .	5 days	"	Dec. 13, 1919	b
V . . .	24 hours	"	Dec. 18, 1919	c
VI . . .	7 days	Lived	Dec. 18, 1919	c
VII . . .	1 day	"	Dec. 19, 1919	a
VIII . . .	3 days	"	Dec. 21, 1919	c
IX . . .	?	"	Dec. 24, 1919	a
X . . .	41 days	Died	Dec. 30, 1919	c
XI . . .	?	?	Jan. 23, 1920	c

Summary. This paper contains a report of 11 cases divided into three groups according to the symptomatology. The first group presented the syndrome of an acute toxic condition; the second group that of a meningitis or meningo-encephalitis and the third group the clinical and pathological findings of epidemic encephalitis. In these cases there was a definite diminution of acuteness in the latter cases and there was an evident contagiousness present in the whole group of cases.

Note. We wish to express our appreciation to Doctors Metcalf, McCrae and Stanley of Fulda, Minnesota, for the courtesy of allowing us to use their clinical records of these cases; to the members of the Division of Communicable Diseases of the State Board of Health for their kindness in making these cases available to us and for the use of their bacteriological and serological records; to Doctors H. E. Robertson and A. S. Hamilton, Chiefs of the Department of Pathology and Public Health and the Division of Nervous and Mental Disease respectively, to Dr. J. C. McKinley for the drawing and to Mr. Henry Morris for the microphotographs.

ANEURYSM OF THE HEPATIC ARTERY: WITH THE REPORT OF A CASE.*

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ANEURYSM of the hepatic artery is a very rare condition, only 54 cases appearing in literature. In 1908, Rolland¹ published a study of 40 cases and at the same time reported a case of his own. In addition the following cases have been recorded and are given in

* Reported by Dr. Thomas McCrae with special reference to the clinical features in the *International Clinics* for September, 1920.

¹ *Glasgow Med. Jour.*, 1908, lxi, 342-358.

the order of their publication: Schupfer,² Bickhardt³ (2 cases), Reichman,⁴ Tuffier,⁵ Dean and Falconer,⁶ Friedman,⁷ Merkel,⁸ Fleckenstein,⁹ Baruch,¹⁰ Teacher and Jack,¹¹ Anderson,¹² and Kading.¹³

No review of recorded cases could be found in American literature.

The condition is interesting also from the viewpoint of its etiology; syphilis does not play the same important part as in aneurysm in general.

CASE REPORT.

The patient, a white male aged fifty years, a plumber, was admitted to the Jefferson Hospital in the service of Dr. Thomas McCrae on March 1, 1920.

Family History. There is nothing of particular importance in regard to his parents, brothers and sisters. He has been married twice. By the first marriage there were four children, all of whom died at the age of three years, five years, two months, and one month but no accurate account of the cause of death can be obtained. His second wife had one pregnancy, which resulted in a miscarriage.

Personal History. The patient as a rule has been very healthy. The only acute illness which he had was paratyphoid fever eight years ago, from which he made a good recovery. As he was in a hospital with this illness and his case was carefully studied the diagnosis is probably correct. He states that comment was made on the diagnosis of paratyphoid fever. Five years ago he had a sharp severe pain in the epigastrium lasting about twenty-four hours. He does not remember much of the details, but is positive that there was no vomiting, and no jaundice following this attack. He has always had some trouble with constipation. There is no history of urinary disease and he denies gonorrhea and syphilis. He has used alcohol very moderately. He has always regarded himself as being an exceptionally strong man. There has not been any change in weight. His occupation is entirely executive and he does not handle lead in any form.

Present Illness. On the day of onset the patient states that he arose at his usual hour feeling perfectly well, took his ordinary very simple breakfast and had been attending to his business all morning.

² Gazz. d. Osp., August 26, 1906.

³ Deutsch. Arch. f. klin. Med., Leipzig, 1907, xc, 289-309.

⁴ Virchows Arch., 1908, xciv, 71-114.

⁵ Presse méd., Paris, 1909, xvii, 153.

⁶ Edinburgh Med. Jour., 1912, n. s., viii, 124-131.

⁷ Med. Rec., 1912, lxxxii, 522-525.

⁸ Virchows Arch., 1913, cexiv, 289-301.

⁹ Inaug. Diss., Giessen, 1913.

¹⁰ Beiträg. z. klin. Chir., Tübingen, 1915, xcv, 502-512.

¹¹ Glasgow Med. Jour., 1916, lxxxvi, 277-285.

¹² Tennessee State Med. Assn. Jour., December, 1919, xii, 286.

¹³ Deutsch. Ztschr. f. Chir., Leipzig, cl, 1-2, 82.

About 1 P.M., while standing on the street talking to a friend, he felt a sudden burning sensation which he indicates as situated in the center of the abdomen occupying a circular space about six inches in diameter with the navel as a center. Almost immediately after this there was intense abdominal pain which he states was in the epigastrium. He thought that he was dying, had difficulty in standing, and broke into a very profuse sweat. He was only a short distance from the office of a friend and with assistance was able to reach it. His serious condition was recognized and the hospital ambulance was sent for at once.

Examination. The patient is very well nourished and has a high color. He is very seriously ill and suffering intense abdominal pain which causes him to writhe about in bed. There is a question as to whether the sclerotics show jaundice and it is best described as icteroid. Examination of the head and mouth is otherwise negative. The lungs are clear. The heart shows a very feeble impulse and no evidence of cardiac enlargement is found. The sounds are distant and feeble; the pulse is 66 and rather small but quite regular. The abdomen is somewhat distended. The patient points to the epigastric and umbilical regions as the seat of the pain. The abdominal walls are soft and do not show any rigidity even in the epigastrium. There is very slight abdominal tenderness on palpation which seems most marked about the navel. The contrast between the severe pain and the absence of rigidity and any marked tenderness is striking. No mass can be felt, and despite the distention it is possible to palpate satisfactorily. The sounds of peristalsis are well heard. When pressure is made over the lower costal region on the right side the patient states that he feels more comfortable. The leukocytes were 13,400.

At the time of admission the condition was very serious, the extremities were cold and he complained of numbness in the hands and feet. Soon after admission he began to vomit. There was no blood in the vomitus but a considerable quantity of bile. Not long after this there was a free movement of the bowels.

The condition improved in the following twenty-four hours and remained much the same during the whole course of the disease. The pain continued at intervals and required small doses of morphin to control it. There was constant fever, which varied, usually being 100° to 102°; the pulse-rate showed slight variation. The jaundice became very definite and rather deepened as the days went on. The leukocytes varied from 13,000 to 17,000; the Wassermann reaction was negative. The stools were negative and showed no evidence of disturbance of fat digestion or the presence of blood. The abdominal pain continued, became more localized in the upper epigastrium and below the right costal margin in the region of the gall-bladder. There was a considerable degree of tenderness in the region of the gall-bladder which gradually increased. As the

patient's condition was not improved, and the signs of local disease in the upper abdomen became more marked, with deepening of the jaundice, exploration seemed advisable. The most probable diagnosis was cholecystitis but it was felt that the picture was not quite the usual one of that disease and that some other condition might be found.

On March 9 at 1 P.M. the patient was carefully examined. There was no abdominal distention and the percussion note in the flanks was resonant. The patient's condition remained the same and at 4 P.M. the anesthetic was begun. After a few breaths the patient died suddenly. No change in his general appearance had been noted. The pulse at the time of beginning the anesthetic was 78.

Autopsy (performed twenty hours after death).

The body is that of an adult white male 70 inches in length, approximate weight 160 pounds. The pupils are moderately dilated and equal. The nostrils are negative. The teeth are in fair condition. The chest is full, the abdomen distended. The external genitals are apparently normal. There is no edema of the limbs. Postmortem rigidity is marked.

The peritoneal cavity contains a blood clot weighing 1600 gms., and considerable free blood. The intestines are constricted in several areas. Liver extends to costal margin in right midclavicular line. Gall-bladder is large and distended. Diaphragm extends to fourth rib on right, and to fourth interspace on left.

Pericardium contains a small quantity of clear serous fluid.

Heart weighs 375 gms. The muscle cuts with increased resistance and is pale red in color. Aortic cusps slightly thickened and stiffened. Mitral, pulmonic and tricuspid valves apparently normal. First portion of aorta contains several light yellow, sharply outlined areas of degeneration. Considerable sclerosis in anterior coronary artery.

Pleura and lungs apparently normal.

Spleen weighs 200 gms. Capsule is grayish. Organ fairly firm and cuts with normal resistance. Trabeculae distinct.

Left adrenal weighs 20 gms., no macroscopic evidence of disease.

Left kidney weighs 190 gms. Organ is large and firm. Capsule strips readily, leaving a smooth surface. At upper pole is a firm, pale red area of infarction measuring 4 cm. in width at base, and extending 3 cm. into kidney substance. Cortex measures 1 cm. in width.

Right adrenal weighs 22 gms. No gross lesion observed.

Right kidney weighs 210 gms., is large and firm, and cuts with increased resistance. Section shows a large, reddish infarct in upper pole, and an anemic infarct in lower pole, each measuring 3 cm. at base (capsule) and 3 cm. in depth. Surface of kidney over the

infarct is raised and dark red. A thrombosed vein is seen at base of red infarct.

Ureters single and patulous. Bladder large and distended with amber color urine. No evidence of inflammation of mucosa.

Duodenum contains yellowish-green material. Ampulla of Vater is patulous; pressure on gall-bladder causes black viscid bile to exude from the common duct.

Pancreatic and bile ducts patulous.



FIG. 1.—Inferior aspect of liver. *a*, aneurysm of hepatic artery; *b*, rod extending from aneurysm along tortuous branch filled with blood clot into liver substance.

Stomach small, thick-walled, rugæ obscured. No evidence of inflammation, ulceration or new growth.

Pancreas weighs 250 gms. Considerable clotted blood about head of organ. Tissue cuts with normal resistance. No gross evidence of disease.

Liver weighs 1680 gms., is large and firm. Surface mottled and smooth; outline regular. Cut surface is mottled and brownish-red. Gall-bladder is distended with black, viscid bile.

Lesser omentum is infiltrated with blood. Dissection shows the hepatic artery at its point of division into right and left terminal

branches to be sclerosed, and dilated into an egg-shaped mass measuring 2 cm. by 3 cm. The wall of this aneurysm has ruptured and its interior is partially filled with blood clot which extends by means of the branches into the liver substance. This rupture into the greater peritoneal cavity is apparently the site of the abdominal hemorrhage.

Aorta. Part of thoracic aorta comprises a cylindric mass 16 cm. in length extending along left side of vessel. On section it is found



FIG. 2.—Outer surface of thoracic aorta from same case, showing dissecting aneurysm. *a*, blood clot lying between *b*, adventitial coat of vessel, and *c*, medial coat.

to be filled with clotted blood, occupying a position between the medial and adventitial coats of the vessel. No opening from the inner side of the vessel can be discovered. The inner surface of the aorta shows several crinkly yellowish nodular areas of degeneration, and many light yellowish striæ. The beginning of the left internal iliac artery is the seat of a fusiform aneurysm measuring 7 cm. in length and 4 cm. in diameter.

Microscopic Diagnosis: Marked congestion and edema of lungs; slight degree chronic interstitial splenitis; marked parenchymatous

degeneration of adrenal; slight hyperplasia of interstitial tissue. Kidney; tubular epithelium is in an advanced state of granular degeneration; that of the convoluted tubules is especially so and in addition swollen and desquamating. Considerable focal and diffuse hemorrhage both into tufts and tubules and interstitial tissue. Supportive structure is definitely increased, and in areas amounts to a patchy fibrosis; here and there are focal collections of small mononuclear cells in the interstitial tissue; "chronic diffuse



FIG. 3.—Inner surface of aorta, showing *a, a, a*, wrinkled patches of syphilitic aortitis.

nephritis." Granular degeneration of pancreas; chronic interstitial inflammation.

Liver: parenchymatous degeneration, passive congestion. Scattered throughout the liver substance and situated especially about the smaller vessels are focal collections of small mononuclear cells. Tangential section of one of the larger vessels shows its partial occlusion by an extending blood-clot. Many of the smaller bloodvessels show an extreme degree of obliterative endarteritis. The walls of the biliary ducts also show thickening and sclerosis, and in areas shedding of the epithelium.

Remarks. The presence of three aneurysms and the rather typical aortitis, together with the microscopic findings of perivascular collections of mononuclear cells, and the well-marked obliterative endarteritis affecting the smaller vessels of the liver, suggest that the process is syphilitic in spite of the fact that sections of the aorta stained by the Levaditi method failed to reveal the spirochete.

A study of the cases in the literature brings out the following points:

Etiology. Aneurysm of the hepatic artery is unique in that a majority of the cases have followed acute infectious processes, especially lobar pneumonia, rather than syphilis. In 26 cases in which the causative factor has been determined with some degree of certainty, aneurysm of the hepatic artery has followed such infections as pneumonia, osteomyelitis and typhoid fever, in 15 cases; syphilis in 5; atheromatous arteritis in 2; cholelithiasis in 2; trauma in 1, and tuberculosis in 1.

Rolland believes that gall-stones may be responsible for the aneurysm by direct injury of the arterial wall, and considers infective emboli as the probable cause in cases following infections. Schupfer reports a case following croupous pneumonia and concludes that the aneurysm resulted from acute infectious arteritis which was produced by the infective agents carried through the vasa vasorum. Grunert¹⁴ considers that 73 per cent. of the 34 cases collected by himself were sequelæ of previous infectious processes.

Rolland believes that syphilis is an important factor and mentions it as directly responsible in the cases reported by Sacquie¹⁵ and Watzold.¹⁶ In describing the changes observed in his case Watzold states that "the arteries show a definite thickening of intima and adventitia; the latter consists mostly of a broad circle of very cellular connective tissue. Almost all vessels show a considerable thickening of the intima which in many instances has resulted almost, or quite, in obliteration." In Rolland's own case changes in the arteries were noted as in the foregoing, and in addition hyalin degeneration of the vessel walls. The case reported by Teacher and Jack showed a widespread patchy subacute inflammatory condition of the hepatic arteries, which has been described as periarteritis nodosa. They state that the cause of this condition is not clear but there is evidence of its syphilitic origin. In addition, the arch of the aorta was thickened and irregular and all solid organs showed a very striking old endarteritis obliterans affecting the smaller vessels, principally those less than 2 mm. in diameter. The cases cited prove that the branches of the hepatic artery may be the seat of a definite panarteritis, as is true in the case under consideration. This condition is undoubtedly a cause of hepatic aneurysm.

¹⁴ Deutsch. Ztschr. f. Chir., lxxi, 158.

¹⁵ Zentralbl. f. path. Anat., 1900, xi, 748.

¹⁶ München. med. Wehnschr., liii, 2107.

Baruch, in his excellent review, states that lues does not seem to be an important factor but that the condition usually follows previous infectious disease, especially pneumonia. The pneumonia usually involves the right side, and Baruch quotes Stumph as stating that in such cases edema of the periportal connective tissue was observed. If there is any connection between this inflammatory process and aneurysm formation it has not been established.

Ross and Osler¹⁷ reported a case in which the patient died with symptoms of pyemia and the liver was found on section to contain multiple abscesses.

Concerning the *age* incidence, Tuffier and Villandre in a collection of 41 cases conclude that the condition is most common in youth. Rolland's review mentions cases from fourteen to eighty-three years, the average age being thirty-seven. Of 39 cases, 30 occurred in men and 9 in women. The average age of 8 female cases was forty-five years; of 28 males cases thirty-five years. Occupation apparently played no part.

Pathology. Rolland divides his cases into extra- and intrahepatic, the majority belonging to the former classification. In his collection 24 were extrahepatic and 8 intrahepatic; and in 2 cases, in each of which 2 aneurysms existed, one was extrahepatic and one intrahepatic. The main trunk of the artery has been affected more often than either of its branches. In 16 cases the main vessel was involved, in 12 the aneurysm was on the right branch and in 3 on the left. In 3 cases an aneurysm was found on each of the branches. In one case an aneurysm involved the cystic artery. In 6 cases the aneurysm was intact; in 32 the sac was ruptured. Rupture occurs in the majority of cases either into the peritoneal cavity or into the bile passages. In 16 cases rupture occurred into the peritoneal cavity, in 13 into the bile passages and in 3 into the stomach, duodenum or portal vein. The aneurysm may undergo spontaneous healing. In one case (Ledieu¹⁸) the aneurysm was occluded by a thrombus, the patient dying of renal disease with no symptoms referable to the liver. Extrahepatic aneurysms are generally larger than intrahepatic. The average size is that of a hen's egg—in one case it was the size of a child's head (Wallmann¹⁹). Sacquiepie was the first to point out the importance of aneurysm of the hepatic artery as a cause of rupture of the liver.

Symptoms and Diagnosis. Teacher and Jack state that in some cases no symptoms referable to the liver occur, but that the aneurysm ruptures before its presence is suspected. In most cases, however, there have been definite symptoms, of which the most common are pain, jaundice and hemorrhage (hematemesis or melena). The striking feature of the hemorrhages is that they

¹⁷ Canadian Med. Jour., July, 1877, vol. vi.

¹⁸ Jour. de Méd. de Bordeaux, 1856, p. 125.

¹⁹ Virchows Arch., Bd. xiv.

recur, frequently with varying intervals between them. It is suggested in explanation that bleeding has occurred into the bile passages and that by rapid filling the bleeding is checked. Severe pain in the right hypochondrium, noted by Rolland just prior to death, is said to have been due to the escape of blood into the substance of liver and the stripping of the capsule of Glisson, rather than to the presence of the aneurysm. In typical cases the pain comes on in paroxysms, and is of great severity resembling that of biliary colic. It is referred to the right hypochondrium and epigastric region. This pain is said to be due to pressure of the sac on branches of the hepatic plexus of nerves. In the case under consideration the pain was sudden in onset and persisted and was probably due to rupture of the intima and consequent tension as sometimes occurs in aortic aneurysm.

Rolland found jaundice in 16 of 40 cases and felt that it was due to pressure on the hepatic ducts or common bile duct. In none of his cases was the incidence of jaundice stated to have any relation to the attacks of pain. Grunert found jaundice in 64 per cent. of his cases and explains its presence as due more to blood in the bile ducts than to pressure of the growing aneurysm, though both are probable factors. Grunert, Hale White⁴⁰ and Schupfer report cases in which jaundice appeared about the twentieth day following pneumonia. The last observer believes that the sudden appearance of permanent jaundice is significant.

Fever is another symptom mentioned as present in a few cases, sometimes accompanied by rigor, reaching 104° and tending to coincide with the height of the paroxysm of pain. Digestive disturbances are commonly present.

In a case reported by Friedman paroxysms of pain of a neuralgic type were associated with visible pulsation over the liver, occasionally expansible, and accompanied by a systolic shock felt over the ribs. A throbbing sensation was felt later when the attacks of pain had become more frequent. A diagnosis of aneurysm of the hepatic artery was made and at operation the surgeon reported "dilatation and elongation of the hepatic artery" which Friedman insists must be considered an aneurysm, or at least an incipient one.

Bickhardt mentions a case in which a tumor, the size of a child's fist, was palpable under the xiphoid. The tumor became fluctuant and three days prior to death a systolic bruit was heard. A differential diagnosis of echinococcus cyst, carcinomatous metastasis and perigastric abscess following perforation of a gastric ulcer, was considered; the autopsy affording the correct diagnosis of aneurysm of the hepatic artery with rupture into the duodenum. He mentions two symptom groups: (1) Jaundice, pain and hemorrhage; (2) cramp-like pains with a palpable and eventually pulsating tumor with a systolic bruit.

⁴⁰ British Med. Jour., January, 1892, p. 225.

Baruch mentions a case in which he had a patient "suffering from cholemia, and internal hemorrhage, and upon exploratory operation, suspecting common bile duct occlusion by tumor or stone, was surprised to find an aneurysm of the hepatic artery." Habs²¹ reports a similar mistaken diagnosis in a patient aged twenty-two years, suffering from chronic icterus.

Baruch states that one will think of aneurysm of the hepatic artery when, in addition to pain and icterus, hemorrhage per orem or anum occurs, but mentions that it may be mistaken for cholelithiasis or duodenal ulcer. "A differential diagnosis is based on (1) young age, (2) male sex, (3) previous infectious disease, especially pneumonia. If the three cardinal symptoms (pain, icterus and hemorrhage) are missing then a differential diagnosis is impossible and the only way to find out would be exploratory incision."

Reichman reports a case associated with pain and hemorrhage, apparent at mouth and anus, but bruit and pulsation were lacking so "no diagnosis was possible."

Treatment. Of 41 cases collected by Baruch only 8 were operated upon and of these but 4 were correctly diagnosed even at operation (Habs, Allesandria,²² Tuffier and Kehr²³). In addition Baruch reports a case in which the diagnosis was made by exploratory incision but fearing liver necrosis he did not ligate the artery. The patient died with symptoms of heart failure. Habs took the same view in his case and performed cholecystectomy and tamponade on the sac. Allesandria incised the sac and tried to stop the bleeding by tamponade but the patient died of exhaustion. Kehr ligated the artery and his patient recovered and he therefore concluded that "every case of aneurysm of the hepatic artery should be ligated, because there is a collateral circulation which has formed during the formation of the aneurysm." Tuffier also ligated; his patient died after passing into coma on the third day following operation. No liver necrosis was present. He believes slow obstruction permits sufficient anastomotic circulation and considers ligation of the hepatic artery the operation of choice.

Baruch cannot accept Kehr's conclusions, stating that experimental work on animals has shown that liver necrosis may occur, quoting Narothe as saying that ligation of the hepatic artery must depend upon the site, "the more central the ligation the more the possibility of recovery." Thus he shows in animals that ligation of the common hepatic artery permits a good anastomotic circulation by the right gastric and gastroduodenal arteries. This is nicely born out in the case reported by Merkel—in which an aneurysm of the common hepatic artery occluded by thrombus permitted a sufficient circulation by means of the vessels named.

²¹ Deutsch. Ztschr. f. Chir., 1904, lxxxi, 158-178.

²² Bull. d. l. Acad. med. di Roma, 1906, xxxii, 63-76.

²³ München. med. Wehnschr., 1903, i, 1861-67.

Baruch summarizes by stating that "a sufficient collateral circulation is present when, if the blood supply of the hepatic artery is ligated or compressed temporarily, a puncture of the aneurysmal sac still continues to deliver blood." If the phenomenon is negative he advises (1) the formation of adhesions by scarifying the posterior and lower part of the liver, and (2) compression of the aneurysmal sac.

Zesas²⁴ in a lengthy discourse on the subject concluded that ligation in any part of the hepatic artery seems the only rational therapy once the diagnosis is made.

Anderson reports a case with operation and recovery in a young man having a previous history of aneurysm of the radial artery. The patient was taken to the hospital in a state of collapse; the abdomen was opened, two quarts of clotted blood removed and a very perceptible oozing noted, welling up in the right lobe of the liver. The hemorrhage was controlled by two mattress sutures and a gauze pack. He states that the hemorrhage undoubtedly occurred from a branch of the hepatic artery. The patient made a very good recovery and with specific treatment gained 30 pounds in four months, only later to develop an aneurysm of the tibial artery and still later gangrene of the toes necessitating amputation.

Summary. 1. Aneurysm of the hepatic artery is a very unusual condition, but 55 cases being recorded in literature.

2. It is of unique origin; infectious diseases playing a larger part in its etiology than syphilis.

3. The main clinical features are pain, jaundice and hemorrhage. Rarely are tumor or bruit present and then only in the terminal stages.

4. Under favorable circumstances the treatment is ligation of the hepatic artery.

PRIMARY SARCOMA OF THE APPENDIX: A CASE OF LYMPHOSARCOMA OF THE APPENDIX WITH ACUTE INTESTINAL OBSTRUCTION IN A YOUNG WOMAN. A REVIEW OF THE LITERATURE.*

BY HYMAN I. GOLDSTEIN, M.D.,

CAMDEN, N. J.

THIERSCH, in 1882, reported the first case (none found previously recorded in the medical literature of the world) of malignancy of the appendix. Thiersch's case was an adenocarcinoma at the junction of the appendix and cecum. This case is described in *Berlin*

²⁴ Fortschr. d. med., Berlin, 1910, xxviii, 1313, 1351-1390.

* Read before the Pathological Society of Philadelphia, June 10, 1920, and the Northern Medical Association of Philadelphia, October 8, 1920.

klinische Wochenschrift, 1882, i, 41. However, primary carcinoma was first recognized and described by Merling in 1838. Many cases of primary carcinoma of the appendix have recently been reported in the literature of the world. There are now on record about 325 cases of primary cancer of the appendix in the entire literature. Primary carcinoma of the appendix is still comparatively rare. Harte in his article states that primary cancer was present in one-third of 1 per cent. of all cases operated on for chronic appendicitis. In 7000 specimens examined up to a few years ago at the Rochester Clinic there was not one case of primary carcinoma of the appendix. Milner believes a condition often recorded as carcinoma is the result of inflammatory proliferation of the adenomatous and endothelial structure of the appendix. Orth and Borst have also pointed out that carcinoma-like formations may follow inflammatory proliferation of such tissues. The majority of cases of primary malignant disease of the vermiform appendix have been recorded since Harte, in 1908, in the *Annals of Surgery*, published a review of all the cases of malignancy to date of writing. He collected, at that time, 120 cases, 114 being carcinomata and 6 sarcomata. Meyer has recently (1915) collected 269 cases of primary carcinoma of the appendix. However, cancer of the vermiform appendix is less frequent than this number indicates, because at the Nicholas Senn Hospital out of 2000 cases one malignant appendix was found, and this was a round-cell sarcoma reported by Michael Wohl, of Omaha, in 1916. Stanley P. Reimann, pathologist of the Lankenau Hospital, Philadelphia, reported 12 new cases of primary carcinoma of the appendix and the 5 previous ones out of a total of 13,151 specimens or about 0.13 per cent. MacCarty and McGrath report 40 cases of carcinoma in 8039. Geist recently reported some rare pathologic conditions of the appendix. Powers in his article mentions the 5 cases Harte described in his paper as sarcomas; Carwardine's (2), a man and a woman; Paterson's (man, thirty-five); Warren's (boy); Guilford's (woman, twenty-seven), and adds his own case (girl, seventeen) and those of T. G. Davis (man fifty-one) and de Jong (adult male). Authentic cases of endothelioma of the appendix have been reported by Glazebrook, Sargent and Sudsuki. Powers reports as questionable the "Sarcomata" of the appendix recorded by Sonnenburg, Murray and Beatson, and concludes by saying (October, 1910) that "Warren's case (in a boy) is practically the only successful case in the series, which, including the case of the writer, numbers 7 instances of primary sarcoma of the appendix."

W. G. Nash reports a giant mucocele of the appendix; M. Cazin, *Des tumeurs endocrines de l'appendice*; carcinoid appendix by Nicolaysen; Bobbio reports a primary carcinoma of the appendix. Crouse in his excellent review of the subject mentions sarcomas of the appendix reported by Sonnenberg, Lamers and Moschowitz and

two myosarcomata by Moschowitz. Boyer reviewed the literature and reported a case of primary carcinoma in 1919.

Cases of primary carcinoma have recently been reported by Darling, Jessup, Macewen, Vance, Tuxen, Braagst, Lahm, Norrlin, Rassieur, Ries, Nigst, Goldstone, Suzuki, Beatson, Mikenda, Bender, Luce, Markoe, Meyer, Ross, Solling, Maresch, Barclay and many others. Rokitansky, Prus, Merling, Mayal, Lichenstein, Leman and others reported cancer of the appendix many years ago.

Primary sarcoma of the vermiform appendix is a great rarity. Up to 1908, Harte, of Philadelphia, was able to find only 6 cases recorded in the entire medical literature of the world, after a very careful search. Garnett Wright, of Manchester, England, in 1911, found 2 other cases, and 1 he recorded, making a total of 9, including Jones's case. In the November, 1910, issue of *Surgery, Gynecology and Obstetrics*, page 466, 11 sarcomas are listed, including 3 doubtful ones.

The first authentic case was reported by Hastings Guilford before the (England) Reading Pathological Society in 1893. This was a case of sarcoma surrounding a concretion in the vermiform appendix. Excision of the cecum was followed by recovery. The patient was a young married woman, aged twenty-seven years. She was always subject to constipation. She was operated upon February 13, 1893. She had three distinct attacks of pain: First in August, 1892, temperature with vomiting and fever (101°). It was thought to be due to uterine cramp. January 30, 1893, she had another attack, with pain around the umbilicus. In this case inflammation existed around the appendix for thirteen years, of a chronic nature.

The first case in America was recorded by J. C. Warren in 1898. Up to Jones's case, 8 cases in all had been reported in the literature, 4 of which were reported in this country.

Jones's case (Seattle, Washington) occurred in a young married woman, aged twenty-six years. She had a mild, recurrent appendicitis, and because of adhesions already existing, extended from the appendix to the walls of the cecum. The patient recovered. Recurrence occurred in Carwardine's case, (1907) here the cecum was also involved. Michael Wohl, of Omaha, reported a case of round-cell sarcoma of the appendix (1916) occurring in a man, aged thirty-five years, a drug clerk. Ten cases, including Jones's, Powers's and Glazebrook's cases were reported up to the time of Wohl's writing, or a total of 11 cases (with Wohl's case) of primary sarcoma of the appendix recorded in the entire medical literature of the world. Wohl, however, did not list White's case (1913); nor those of Davis, de Jong, Smit and Wright—a total of 5. Wohl's case was confirmed by Dr. Frank Hall and M. Petit.

L. Smit reported a case of sarcoma of the appendix in a soldier, aged forty-four years, in the *Medical Review*, Bergen, 1916, xxxiii, p. 377 (Norway). The case of de Jong (1908) occurred in an adult

male. The appendix contained a small fecal concretion in its central portion and at its tip there was a tumor the size of a hazelnut.

Powers's case (Denver) was reported before the Colorado Medical Society at Colorado Springs, October, 1910 (by Dr. Charles A. Powers, of University of Denver). This case occurred in a young female patient (Miss B.), aged seventeen years. She suffered from a fairly typical attack of acute appendicitis five weeks before operation. Lost fifteen pounds in five weeks. She was again seized with a sudden attack of abdominal pain, and vomiting repeatedly. W. B. C., 14,000; operated upon on March 15, 1910. Appendix examined by H. S. Denison, of St. Luke's Hospital, and confirmed by Dr. William Welch, of John Hopkins Hospital, Baltimore. She steadily lost flesh. Systemic injections of Coley's toxins were given for the general sarcomatosis which resulted from the initial growth. Patient died May 23, 1910, ten weeks after operation. T. G. Davis's case occurred (1900) in a man, aged fifty-one years. He had suffered for twelve months. After operation it was found to be a small round-cell sarcoma. In his paper Wohl excludes Glazebrook's case (endothelial sarcoma) because he thinks it probably an inflammatory tumor resulting from proliferation of the endothelial lining of the lymph spaces. Kelly and Hurdon ruled out the case of Guilford and Rolleston, and Jones excluded Bernay's case. However, Wohl includes these last 2 cases in his total of 10 cases of sarcoma of the vermiform appendix found recorded in the entire medical literature of the world. Warren's case occurred in a child, aged six years. Carwardine's first case was a female patient, aged forty-five years, the other occurred in a man, a case of primary lymphosarcoma of the appendix. Bernay's case was twenty-nine years old, a female patient. Paterson's case was a man, thirty-nine years of age, round-celled sarcoma. Glazebrook's case was a colored man, fifty-five years of age. In (George D.) Stewart's case the man was thirty-five years old, had his first attack of appendicitis a year before operation; he had pain over the appendix, a second attack three months before operation and a third attack two months later. On the day of operation he was taken with severe pain and persistent vomiting. W. B. C., 16,000 to 12,200. Operation, February 1, 1908. Harlow Brooks made the examination and the pathologic report of Stewart's case and called it fibrosarcoma (spindle-cell sarcoma).

Nothnagel does not note a single case of primary sarcoma of the appendix. Jones, of Seattle, says: "It is an extremely rare occurrence." In Warren's case the patient was well and free from recurrence four years after operation. This is striking evidence of the apparent slight malignancy (at times) of these growths as compared with those in all other parts of the alimentary canal. Results of operation, both immediate and remote, have been good. Inflammatory changes, either chronic or acute, very frequently

accompany the growth. The fact that primary sarcoma of the appendix may take its origin in an inflammatory process forms a very strong additional argument (Wohl) for the removal of all appendices which show evidences of inflammation. Zaaier comments upon the preceding existence of chronic appendicitis as an important factor in the etiology of malignancy of the appendix. He also calls attention to the youth of the patients. In the very few cases reported (17) the tumor has been comparatively small and the diagnosis was made only by microscopic examination of the specimen. According to White and Whaland it has been difficult to state whether these tumors have accompanied an inflammatory process or followed it, or whether they have resulted from an entirely independent process (sarcoma) that has later caused inflammatory change. Sarcoma is classed as a connective-tissue tumor, but unlike other connective-tissue tumors the cells do not advance beyond their embryonic state but multiply as such. Wright, in his analysis of the 9 cases recorded at that time, states that in a majority of the cases the growth was a round-cell sarcoma, 4 classified as round-cell sarcoma and 2 as lymphosarcoma. He suggests that it is possible that all were really examples of lymphosarcoma; 1 was called an endothelial sarcoma and 2 were classified as fibrosarcoma or spindle-cell sarcoma, but in both these latter cases inflammatory changes were present and the diagnosis seems to be doubtful. Wright's case occurred in a boy, aged seventeen years (January, 1909), recovered, and in good health two and a half years after operation. Wohl states prognosis in sarcoma of the appendix is less favorable than in cancer, while in the latter metastasis and recurrence is the exception, in sarcoma only 3 cases have remained free from recurrence, 4 cases have developed recurrence followed by death and 1 case died six hours after operation. He concludes sarcoma of the appendix, especially the round-cell type, is highly malignant; and that it is a rare condition—only 10 cases recorded in the entire medical literature of the world.

In 840 appendices examined at the Episcopal Hospital, Philadelphia, from January, 1918, until the time of writing the 1913 reports, one case of sarcoma of the appendix had presented itself. White's case occurred in a young woman, E. F., aged twenty-five years. Her chief complaint was abdominal pain and vomiting. Operation, September 18, 1909, by Dr. Harry C. Deaver. According to White and Whaland's analysis (1913) the type of cell found in the reported cases varied, viz.; small round cell, 8; spindle cell, 3; lymphosarcoma, 1; fibrosarcoma, 1; small round cell (White's case), 1.

Hugh Crouse, of El Paso, Texas, reviewed to 1910 the literature on "Tumors and Retention Cysts of the Appendix," and mentions and lists all the cases of carcinoma, sarcoma, myxoma, fibromyoma, cysts and myosarcomata of the appendix that he found in the

literature up to 1910, since the first malignant appendix was recognized and described by Merling in 1838.

Clarence Webster, H. A. Kelly, Moschowitz, Goffe, Isaac, Coons, Wahlgren, Letulle, A. O. J. Kelly, E. H. White, McWilliams, Zaaier, Wolskler, Burnam and Le Conte reported cases of primary cancer of the appendix. Fischer, Reel, Parker, Chevier, Moore and Palieri reported cystic tumors of the appendix; Ogilvie, a pseudomyxomatous cyst; Phemister, a pseudomucinous cyst; Stickney, a myoma; Tyler, a colloid cyst; Beatson, carcinoma in a girl, aged twenty years; J. Halban, carcinoid growths; Ombredanne, aged eight, a myxoma; L. D. Redway, a leiomyoma; Tagliavacche, fibromyoma and actinomyces; Moore, cysts; Bailey, pseudomyxoma; Battle, sarcoma of ileum in a girl aged eight years. Carwardine treated his patients in 1905. Shattock, who examined the specimen, called it lymphosarcoma, having its primary origin in the submucous tissue and tending to infiltrate the neighboring coats, as is common with lymphosarcoma of the alimentary tract. He mentions Paterson's and Warren's cases as the only 2 found recorded in the literature to 1907, and quotes H. D. Rolleston and Lawrence Jones to that effect. Crouse lists the following cases and articles on the subject of sarcoma of the appendix, including some that have not been accepted, being considered as questionable by various writers: Sarcoma, H. A. Kelly, 5 cases (mentioned in his Book, 1905); Lamers, 1 case; A. C. Bernays, 1 case; Sonnenberg, 1 case; Moschowitz, 2 cases; Guilford, 1 case; Rolleston and Jones, 2 cases; Warren, 1 case; Carwardine, 1; Paterson, 1 case; Moschowitz (myosarcoma) 2 cases.

At the Mt. Sinai Hospital, New York City, up to June, 1908, there were examined 2700 specimens, and among these were 8 cases of primary carcinoma of the appendix. He (Moschowitz) mentions as "peculiar" about carcinoma of the appendix that they occur in the very young, and he mentioned before the New York Obstetrical Society at the time of this discussion a case in a young girl, aged ten years.

The diagnosis of sarcoma of the appendix cannot be made in the early stages from the symptoms. All the cases resembled attacks of appendicitis. The prognosis is good if the tumor is small and situated some distance from the proximal end of the organ, and when adhesions and involved glands are not present. Sarcoma of the appendix is usually of the small round-cell type, which is generally of rapid growth, infiltrating and tending to rapid metastasis. The adjoining head of the cecum and the draining lymphatic glands should always be very carefully examined and their condition determined. In about one-half of the malignant appendices (carcinomata and sarcomata) the growth is found at the distal end of the appendix. Most of the patients are young, the greater number occurring in the female.

Treatment consisted of simple appendectomy and resection of enlarged glands of the mesoappendix when malignancy of the cecum and appendix was suspected by the surgeon. Le Conte mentions the fact that simple removal of the appendix (cancer) is sufficient to bring about a cure. The good results are explained by Crouse as probably being due to the early symptoms and early operation in primary malignancy of the appendix vermiformis. Wells comments on the youth of the patients and states that he was able (1908) to find only one case which had died of carcinoma existing only at the appendix.

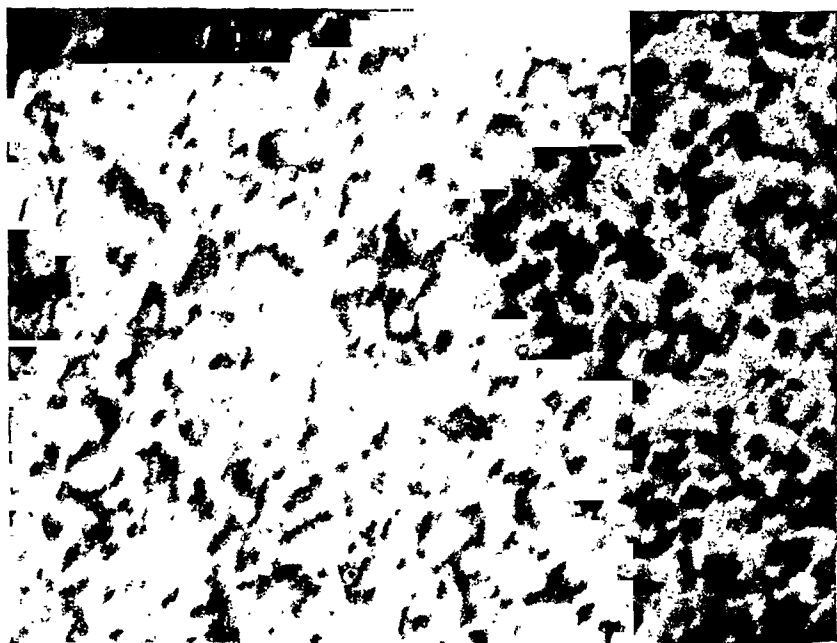


FIG. 1

Case Report. Miss Lena G., aged twenty-five years; white girl. Resides in Camden, New Jersey.

Family History—Negative. Worked in pen factory for a number of years. I was called in to see her for the first time on September 29, 1919, at 10 P.M. She said she was an inspectress of pens and was piercing the slits and cuts in pens for eight years. She was always very constipated and had "stomach and bowel" complaints for several years. She had swollen feet and legs several years ago; had measles and "rheumatism." Lost 23 pounds in the past two years, most of it during the past few months. Her best weight was 123 pounds; now weighs only 100 pounds. She has had several similar attacks of "appendicitis," with severe pains, abdominal cramps and vomiting during the past four or five years. Present

attack of "pain in the stomach" and vomiting began two days ago, and a physician who was first called in diagnosed the case as acute appendicitis. The vomiting was persistent and severe and the pain became worse. Abdomen was distended and rigid; pulse rapid; temperature, 100.5° ; patient looked "very sick." There was a peculiar fulness and distention in the upper abdomen, and marked pain and tenderness and rigidity very low down in the right iliac fossa. While the case gave all the appearances of a severe acute appendicitis, with probable abscess formation and adhesions due to previous attacks of inflammation in this region, yet it also looked

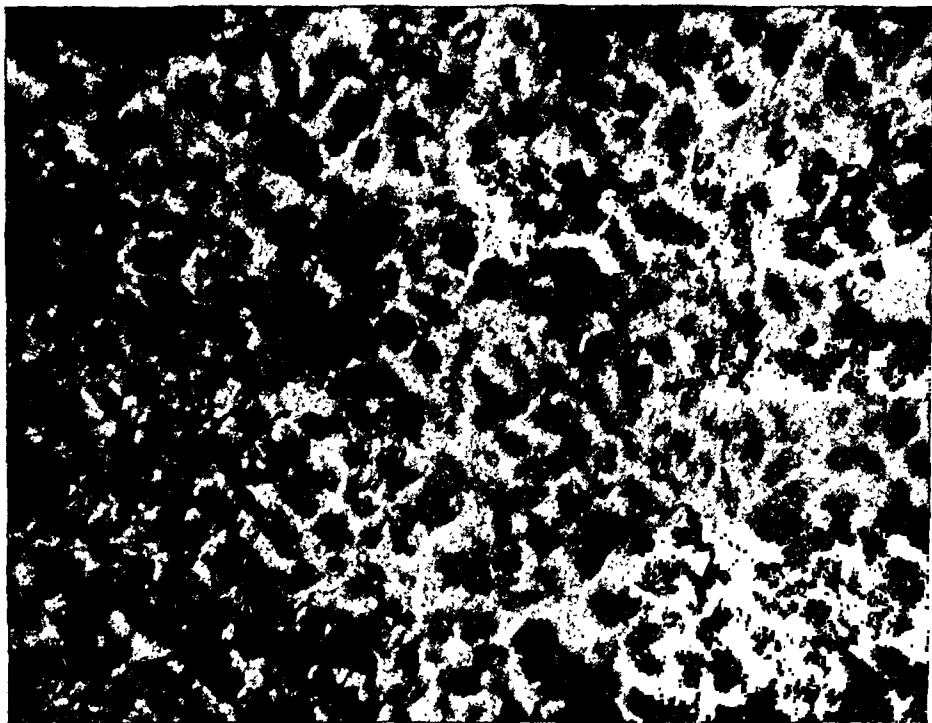


FIG. 2

like a typical case of acute intestinal obstruction, with or without some acute inflammation, and involvement of the right tube and ovary. I advised immediate removal to the hospital for operation. The patient and her family wanted to talk it over, during the night, so I left the house. Early the next morning, September 30, 1919, I was urgently called on the telephone, to come to the house at once, as the patient was much worse, the pain more severe, and the vomiting constant. I found the patient in bad shape, with markedly distended and painful abdomen. I immediately arranged with Dr. Alfred C. Wood, of the University of Pennsylvania and Howard Hospitals, Philadelphia, for prompt operation. Dr. Wood saw her, within two hours after I left the patient's house, at the Howard Hospital. He also thought there may be intestinal obstruction

with the diseased appendix. Under ether anesthesia Dr. Wood opened the abdomen and found the appendix diseased, with a mass involving the appendix and the head of the cecum; the mass in the cecum could be distinctly felt, but was thought and hoped to be inflammatory in nature. Appendectomy was quickly done, as the patient was very weak, and the cecum left untouched for the present. The gut was markedly congested and distended with gas and forced outside of the incision. On searching for a possible obstruction a thick band was found tightly constricting the gut low down in the right iliac fossa, and a foot of bowel was dark and quite

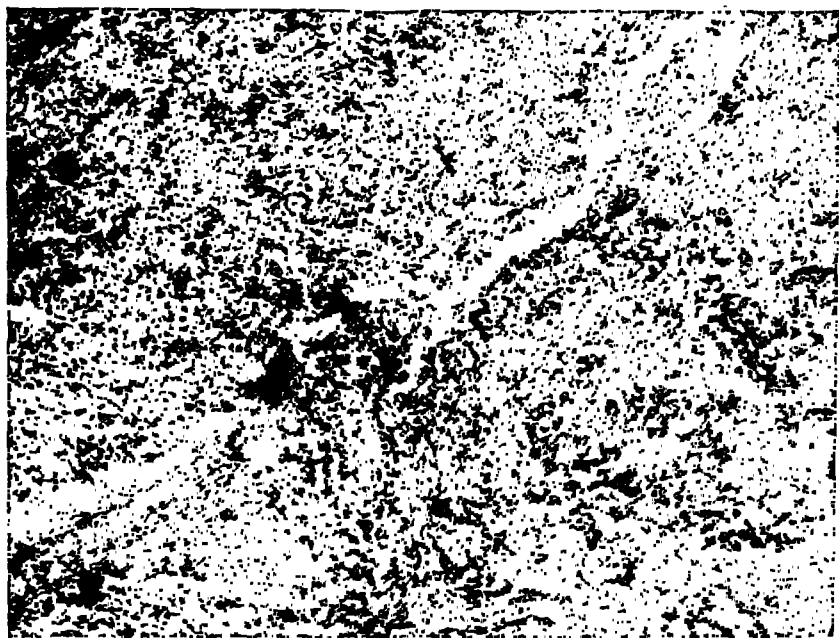


FIG. 3

discolored; the strip where the band was holding was nearly black and gangrenous; however, upon release of the band and the application of hot wet compresses, the color improved, and as the patient was very weak, Dr. Wood and I felt enough had been done; the distended gut was therefore, with some difficulty, replaced into the abdominal cavity and the wound sewed up, and the patient was returned to her private room. The appendix was sent by Dr. Wood to Professor Allen J. Smith, pathologist of the medical department of the University of Pennsylvania, and he made a very careful examination of the tumor and the report of lymphosarcoma of the appendix was received from him (October 21, 1919, Block, No. 6239), and is here appended. The "mass" in the cecum cannot be felt at present (May 26, 1920); this was probably inflamma-

tory in nature, and probably not the same as the real tumor in the appendix. The patient is well and able to do her work, eight months after the operation. She has not regained her best weight and is still very costive. She has no pains and feels "no mass." Has no cough nor chest symptoms, no palpably enlarged lymph nodes. She says she weighs about 100 pounds and has some abdominal distention when "her bowels do not move for a day or two." Her mother recently had an attack of biliary colic; she is fifty-three years of age and has had "gall-stone trouble" for twenty years. I saw the patient and her mother May 26 and June 1, 1920.

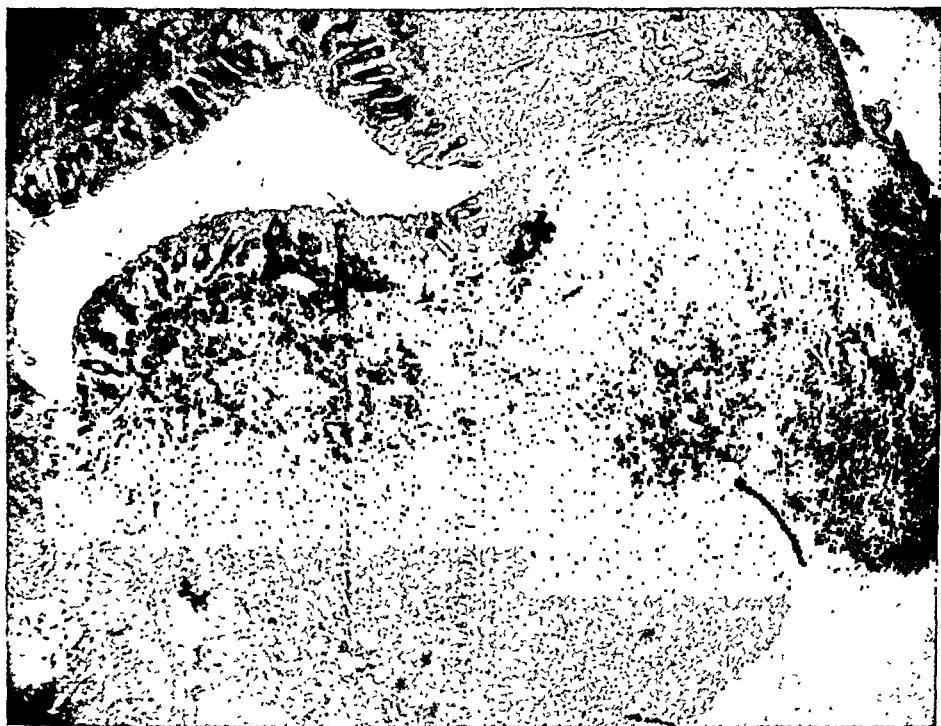


FIG. 4

Report of Specimen Examination. Name and address of the patient: Lena G., Camden, N. J.

Diagnosis: Lymphadenoid sarcoma of the appendix.

Section of appendix in proximal, thickened, portion above the tube here of approximately 1 cm. in diameter, the thickening involving to some extent all of the circumference of the wall, but particularly that half next the mesoappendix, which is over 5 mm. in thickness (that of the opposite side being about 1.5 to 2 mm. thick). The lumen in the section is open but compressed by the swollen side of the wall to a crescentic outline. Under low magnification (under a hand lens) the thickening referred to seems due to a fairly defined mass under the broken mucosa, apparently involving both sub-mucous and muscular coats and extending into a thickened meso-

appendix. With higher magnification this mass is found fairly sharply defined but not encapsulated, and to be composed of small round cells of lymphocytic type, not arranged with any special architecture, infiltrating the deeper tissues, but apparently partly limited to the overlying mucosa. At its borders the cells infiltrate the adjacent tissue of the submucosa and deeper coats; and in its extension through the wall it infiltrates the muscular coat irregularly.

The mucosa is relatively normal, broken at one or two points by artefact and not ulcerated; its glands of about normal size and showing a slight excess of goblet cells. Its follicles are large, solidly lymphocytic; and at its base throughout the circumference there is a continuous excess of lymphoid cells, suggestively extending from the lymphocytic mass above referred to. In the half of the wall not occupied by the nodule the submucosa is thickened, fibrous but loose, with the node showing a narrow zone of infiltration on each border into the coat. The same is true of the muscular coat and of the fibroserous tunic, but in the node itself the muscle can be traced, its fasciculi separated well by the lymphoid cells. The fibroserous coat is dense and slightly thickened at places, elsewhere thick and loose as from edema, and throughout contains a scattered excess of lymphocytes.

There is a second section of a loose fibromuscular tissue (smooth muscle) which is believed to have been part of the mesoappendix, which does not show the structure of intestinal (colon or appendix) wall. In this as well the lymphocytic formation is massively infiltrated in part of the tissue, the rest of the tissue showing a loose, rich infiltration by the same type of cells and small foci of the same elements.

In studying this lymphocytic formation it is to be recalled that it has formed in one or more nodules, not encapsulated but with narrow zones of infiltration at the borders, with scattered excess of the same type of cells through practically all of the sections; that it does not present the architecture of a normal or of an inflamed lymph node, being without follicles and sinuses; that the cells are contained in a delicate lymphadenoid reticulum. The cells are almost all of the ordinary appearance of small lymphocytes, but scattered among them are larger lymphoid examples, and that at places there is the appearance of elongation of these cells into spindle form and small fibroblasts as if some degree of organization were proceeding at such sites. There are too at places eosinophiles to be seen. The small mass is fairly vascular, the vessels of capillary type.

From the above data the writer is satisfied that there is a chronic inflammatory involvement in the changes of the appendix, but believes that the nodular thickening on one side of the appendicular wall is not of inflammatory origin, not to be a lymph node occurring aberrantly in this situation, but by exclusion has come to the view that it is a true tumor, a lymphadenoid sarcoma.

Conclusions. 1. While carcinomata of the appendix have been more frequently reported during the past fifteen years, they are still comparatively rare.

2. Sarcoma (primary) of the appendix of any type is a very great rarity.

3. That the following are the only authentic and accepted cases of primary sarcoma of the appendix found recorded in the entire medical literature of the world: Those of Guilford, Warren, Patterson, T. Carwardine (2 cases), de Jong, T. G. Davis, Powers, Rohdenburg, Wohl, Smit, White, Stewart, Jones, Bernays, Wright and the author's case—a total of 17 cases, if we accept all these cases, and exclude Glazebrook's case, of sarcoma of the appendix in the entire literature of the world.

4. All the cases showed symptoms resembling attacks of acute or recurrent appendicitis. It is impossible to make a correct diagnosis before operation.

5. All appendices removed at operation and at autopsy should be carefully examined; there may be more malignant appendices found which at present escape, because of failure to examine them carefully in the laboratory.

I wish to express my thanks to Prof. Allen J. Smith,* for the preparation and the careful examination of the slides and for making the three illustrations (photomicrographs) and the complete report; and to Dr. A. C. Wood, for the prompt operation, and for sending the specimen to the medical laboratories of the University of Pennsylvania for study immediately after the operation.

Addendum: Primary Sarcoma of the Appendix. Rohdenburg of the Lenox Hill Hospital, New York City, has reported a case of primary lymphosarcoma of the appendix occurring in a child, aged four years. In his report before the New York Pathological Society he stated that after a thorough search of the literature he found his to be the "first case of a lymphosarcoma of the appendix." Ten months after the operation the patient is still alive and apparently healthy. No other evident tumor process was found in the abdomen at the time of the operation. Microscopic examination showed a typical lymphosarcoma involving all the coats of the appendix extending into the mesoappendix and infiltrating the cecum. The growth showed the usual signs of an acute suppurative infiltration.

Brinkmann, on November 16, 1920, before the St. Agnes Hospital Clinical Society, Philadelphia, reported a case of primary sarcoma of the small intestine. While the appendix was not found to be seriously involved, the actual mass consisting of a hard, flat growth was found about three inches from the ileocecal valve, which produced (partial) obstructed interference to the passage of the bowel contents.

* Prof. Joseph McFarland, Prof. Milton B. Hartzell and Dr. Frank B. Lynch, of the University of Pennsylvania, also examined the slides and confirmed the diagnosis.

The patient was a child, aged eight years, who had three attacks of what appeared to be acute appendicitis, with recurring attacks at intervals of two weeks. Dr. Brinkmann saw the patient with Dr. Blumberg in the third attack. Diagnosis was made of acute appendicitis, probably gangrenous, the appendix enveloped with omentum. At operation the appendix was found not to be seriously involved. The mass, situated three inches from the ileocecal valve, was resected. No other demonstrable lesions were found in the abdominal cavity. The operation was performed on February 22, 1920. The patient made an uneventful recovery. Her general appearance indicated health. She was of normal stature for her age and of normal weight. At present, nine months after the operation, abdominal examination is negative. Roentgen-ray examination made at the St. Agnes Hospital is also negative. The passage of an opaque meal was uninterrupted.

Brinkmann states that while it is true the time is too short to predict a complete recovery without recurrence, he feels from the pathologic examination that her chances are bright. The section as shown under the microscopic examination, demonstrates invasion of the mucus and submucus coats only, the peritoneal coat being normal at the periphery of the resected portion of the gut.

NOTE.—Dr. Brill, of the Mount Sinai Hospital, New York City, some time ago, at a meeting in Albany, reported a case of sarcoma of the duodenum which disappeared spontaneously. Dr. Stengel, of the University of Pennsylvania Hospital, Philadelphia, told me of an interesting case he had in a woman, aged thirty-five years, in whom at operation a large sarcoma of the stomach was found, the stomach wall being over three inches thick. In both cases they were thought to be *primary sarcoma* of the gastro-intestinal tract.

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INFLUENZA AND EPILEPSY: FURTHER STUDIES UPON THE RELATIONS OF MENTAL DISEASE AND INFLUENZA.

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WHAT effect has influenza upon idiopathic epilepsy?

Hippocrates is cited as saying that "acute fevers can influence epilepsy both favorably and unfavorably."³ Of course, Hippocrates did not know of influenza, or at least not by its present name or reputation. When one recalls that acute infections have sometimes seemed to improve or even cure epilepsy, as well as some psychoses²³ and even hypophrenia,³⁵ it is the more pertinent to inquire if, after all, the influenza epidemic may have accomplished at least this morsel of good or if, on the other hand, it was as we supposed, "An ill wind that blows . . . etc."

Yet, strangely enough, the matter has never aroused much interest. Literature on the topic is remarkably scant. There were a few scattered communications on the general subject of epilepsy associated with the influenza epidemic of thirty years ago, and to date one¹⁰ discussion of the subject in relation to the 1918 epidemic and one case report; the interim is barren.

Study of the question is facilitated by the large amount of material afforded by the epidemics of influenza of 1918 and 1920. Intramural ravages of the epidemic were experienced in most of the institutions for the care of epileptics in this country. Questionnaires addressed by the writer to the superintendents of these institutions were very courteously treated and the responses were gratifying. However, the severe crippling of the medical staffs as well as of the employee force as a result of war, influenza and price inflation made impossible the detailed notes and observations which would have been desirable. Pertinent data and cases from these replies are cited. In addition to these data I have certain cases for report taken from our Boston series² (the Psychopathic Hospital), from which we have presented previous studies of the relations of influenza and mental disease. I have emphasized³⁵ that it is not because influenza is so important *per se* that its relations to mental pathology have been thus the object of our persistent analysis, but because influenza furnishes us with a ubiquitous and tangible somatic factor.

The exact status of the somatopsychoses is perhaps as tenuous as that of any of the major groups of mental disease, and it behooves us to regard, with an extraordinary interest, any data available to further our knowledge concerning the interrelations of mind and body; or, better, of brain pathology and body pathology. What little has been achieved in this direction in the past has been done

by similar studies of typhoid fever, malaria, etc., diseases which could never compare in ubiquity with influenza, and which, thanks to the efforts of preventive medicine, are so rapidly decreasing as to be no longer sources of psychiatric study.*

Delasiauve⁴ as early as 1854 considered the subject of epilepsy and acute infections. He discusses the influence of various infections, *omitting influenza*, and decides for a specific effect for some (*e. g.*, erysipelas, he thought, improved epilepsy, whereas typhoid augmented the manifestations). He cites many writers and many cases of his own, and concludes in general, on this point, that "all severe and acute illnesses suspend or weaken epileptic fits and chronic ailments diminish them." Veyssset⁵ undertook a detailed historic review and cites 6 cases, but nowhere refers even indirectly to influenza. Seglas⁶ wrote at length concerning the influence of almost every sort of thing upon epilepsy—measles, scarlatina, fractures, erysipelas, malaria, etc.—but he nowhere makes mention of influenza. Certain of his conclusions are worth quoting here, however, even with this pertinent omission: "Intercurrent maladies have in the majority of cases a favorable influence upon the course of epilepsy. . . . This influence may not be manifested during the course of the intercurrent disease. . . . The acute diseases with febrile reactions bring about the most perceptible modifications."

Perhaps the most spectacular account of the effect of febrile affections upon epilepsy is that of Turnowsky,⁷ of Marosvasarhely, who cites 3 cases of established epilepsy in which seizures were never again seen (six to fourteen years' observation) after attacks of pneumonia (two) and scarlatina (one). He is enthusiastic enough about these observations to suggest the possible therapeutic advantage in epilepsy of exposure to scarlatina or pneumonic infection.†

Upon recourse to the text-books one is again disappointed. Oppenheim⁸ remarks that "acute febrile diseases often serve to inhibit the convulsions (of epilepsy), and recovery may even in a few cases be due to this cause." But his only mention of influenza in this regard is to cite (upon another page, 1215) an instance of reprecipitation of attacks, to be referred to later. Most of the writers are content to make some such ambiguous statement as

* Recently Paulian²⁵ has made a detailed study of typhus fever; Skoog²⁷ recently reported briefly on measles. There has been rather more tendency of late toward psychiatric analyses of the endocrinopathies such as Raeder's²⁸ recent report on the endocrinopathic aspects of feeble-mindedness. All of these efforts are valuable because they give us additional data in the consideration of the broader question of somatopsychoses as a group.

† Whatever opinion one may form of this proposal, Turnowsky's suggestion of the possible application of the analogy of the phenomena of reinforcement and interference of the waves of light and of sound to the intercurrent of pathological entities is worthy of attention. The great principle of analogy is rather likely to be applied, we think, too closely within the separate (?) spheres of scientific study, and this wide flight of Turnowsky's, for all its novelty, certainly has merits of originality and perhaps of faithfulness.

this, from Paton:⁹ "The relation of the acute infectious diseases to this psychosis (epilepsy) has been repeatedly emphasized by clinicians—measles, diphtheria, typhoid, as well as whooping-cough, scarlet fever and malaria."

I. EVIDENCE THAT INFLUENZA MAY IMPROVE EPILEPSY.

That there is often observed a cessation of attacks during the height of the acute illness has been commented upon by various writers, some of whom have been quoted. Maillard and Brune,¹⁰ in addition to pointing out the increased susceptibility of epileptics to influenza, put emphasis upon the "almost complete suppression of attacks during the period of acute (influenzal) illness" in all their cases. They found that the average total number of attacks was lowered from 105 daily prior to the epidemic to 14 attacks daily during the febrile period. "The curve of attacks in the course of the influenzal infection is absolutely characteristic in all of our observations, an arrest of the epileptic by the influenzal process."

Similar observations were made in this country. Dr. H. B. Carriel, managing officer of the Dixon (Illinois) State Hospital, replied to the question of the effect of influenza upon the epileptics in his institution as follows:

"It was not found that the disease had any permanent effect upon the epileptics. It was noticed, however, that of those suffering from influenza almost none had seizures (of epilepsy) during the attack (of influenza). This was especially true during the time that their temperatures were abnormally high or subnormal."

This fact is also pointed out in a letter from Dr. David Fairchild Weeks, superintendent of "The Village for Epileptics," at Skillman, New Jersey. "During the time the patients had a rise in temperature they did not have convulsions."

The following case is one studied at the neurological clinic of the Boston Dispensary (then in charge of Dr. Abraham Myerson), where the writer was an assistant visiting neurologist. The case is reprinted in abstract from a previous communication dealing with mental diseases associated with influenza.¹¹

CASE 1.—Family History. A white school boy, aged fourteen years, had a father who was subject to outbursts of temper, and a mother who was subject to chronic headaches. One sister is living and well.

Past History. Unimportant.

Epileptic History. In August, 1916, he had a sudden epileptiform seizure, quite typical in form. They recurred frequently thereafter, averaging one a month.

Present Illness. In September he contracted severe influenza. During his illness he had three, possibly four, more seizures. The

last was on October 21, while he was still bedridden. Thereafter he was seen in the nerve clinic frequently and had no more seizures. (Seen January 14). A physical examination was entirely negative and a Wassermann test on the blood serum was negative.

INSTITUTIONAL DATA. Dr. William T. Shanahan, of the Craig Colony for Epileptics, at Sonyea, New York, in a most comprehensive summary, writes:

"Six patients (one male, five females) had *fewer* seizures *during* the period of influenza and a period of *three weeks before and three weeks after* the attack than their usual wont. (This is contrasted with twenty-five patients who had more.)

"Seven patients (all females) had *fewer* attacks per month for the *next nine months after* the influenza than for the preceding months (contrasted with sixteen patients who had more attacks.)"

Dr. Shanahan kindly furnishes the following representative abstracts, as illustrative:

CASE 2.—Agnes S., aged seventeen years, an epileptic for eight years. Monthly average seizures for nine months before influenza, sixteen. During October and November, when she had a moderately severe influenza, ninety-three seizures. Monthly average during nine months following this period, eight.

CASE 3.—J. S., female, aged ten years, epileptic since seven months of age. Monthly average for nine months before influenza, ten seizures. During October and November, when influenza occurred, twelve seizures. Two of these occurred while in bed with influenza. Monthly average of seizures for nine months following influenza, five.

CASE 4.—W. S., female, aged twenty-eight years. Epileptic for twenty-four years. Monthly average for nine months before influenza, six seizures. During October and November, eight seizures, three occurring while ill with influenza. Monthly average for nine months following influenza, four seizures.

For the following 2 cases I am indebted to Dr. O. S. Hubbard, superintendent of the Kansas State Hospital for Epileptics at Parsons, Kansas:

CASE 5.—"Miss H., an epileptic imbecile, has been in the hospital fifteen years. She comes from a defective family. Her seizures usually occur in series at long intervals. She is of the noisy talkative kind, who irritate those about them by persistent conversation. She was extremely sick with influenza, and while she had no distinct pneumonia, had respiratory difficulty. For a number of days her fever remained about 105°, and that gradually subsided. While her fever was high she was much more quiet and talked in a rather

intelligent manner—in fact, seemed another personality, almost normal. With the improvement in her health her mind returned to its former standard and she is in every way much as she was before being sick.”

CASE 6.—“Mr. W. had been a patient of the institution for a number of years. For a considerable period he was on parole, and under excessive sedation in the form of patent medicine he became much reduced in health. He contracted influenza which was complicated by pneumonia, from which he made a good recovery. He improved markedly both physically and mentally. One forenoon he had five grand mal seizures in quick succession and following them developed edema of the lungs, from which he died that evening.”

II. EVIDENCE THAT INFLUENZA MAY AGGRAVATE EPILEPSY.

Aggravation of epilepsy may be conceived of as taking any of four forms:

1. Simple increase in severity and frequency of attacks.
2. Reprecipitation of long latent epileptic attacks.
3. Alteration in the form of the attacks.
4. Production of a complicating psychosis.

Illustrations of each of these are at hand.

1. INCREASED FREQUENCY AND SEVERITY OF ATTACKS AFTER INFLUENZA. The suppression of attacks of epilepsy during the acute period of illness (influenza) as discussed above is not stated by any of the writers or any of my communicants to have been permanent. So much for negative testimony. On the other hand, Dr. Shanahan writes:

“One patient had status epilepticus during the height of the influenza.

“Twenty-five patients (5 males, 20 females) had more seizures *during the period of the influenza* and a period of three weeks before and three weeks after the disease” (than their average wont). (This is contrasted with 6 patients who had fewer seizures at Sonyea.)

During the *nine months* which have passed since the epidemic 11 males and 5 females who had the disease have shown an increase in the frequency of seizures. (These 16 patients contrast with only 7 who showed a decrease in frequency of attacks.)

Dr. Shanahan also furnishes the following abstracts of cases illustrating the above stated increase in frequency:

CASE 7.—E. Z., female, aged twenty years, an epileptic for ten years. Monthly average for *nine months before influenza*, twelve seizures. During October and November, eleven seizures. No

seizures while in bed with influenza. Monthly average for nine months following influenza, sixteen seizures.

CASE 8.—E. V., female, aged twenty-two years, epileptic since early infancy. Monthly average for nine months before influenza, twenty-six seizures. During October and November, fifty-two seizures, nine of which occurred while ill with influenza. Monthly average for nine months following influenza, thirty seizures.

CASE 9.—Jacob F., aged twenty-two years, epileptic eighteen years. Average from four to ten seizures monthly for nine months preceding influenza. During influenza period seizures continued with same frequency. During nine months following influenza, seizures were more frequent, averaging thirteen to sixteen per month.

CASE 10.—Albert P., aged fifty-five years, epileptic for forty-two years. For nine months preceding influenza had but four seizures. During influenza period had eleven seizures. During nine months subsequent to influenza averaged two or three seizures each month.

CASE 11.—John R., aged thirty-four years, age of onset unknown. Patient at the colony for twenty years. For nine months preceding influenza, period averaged five to six seizures monthly. During influenza period had fifteen seizures. During nine months following influenza period has had from seven to ten seizures on average per month.

CASE 12.—Charles G., aged thirty-six years, epileptic twenty-one years. For nine months preceding influenza period had average of one seizure per month. During influenza period had twenty-one seizures. Since influenza period had averaged from six to eight seizures per month.

CASE 13.—Fred P., aged thirty-eight years, epileptic since ten years. For nine months preceding influenza averaged ten per month. During influenza period had fifty seizures. During nine months following influenza period has had an average of thirteen seizures per month.

2. REPRECIPITATION OF LONG LATENT EPILEPTIC SEIZURES. Another phenomenon of aggravation is the precipitation of a recurrence of attacks in a patient previously frankly epileptic but in whom supposed recovery or long remission had occurred. This is not infrequently casually referred to in the literature, but I do not know that it is anywhere critically discussed. Oppenheim⁸ cites the case of "G, a neuropsychopath," who had suffered from "conditions of anxiety and imperative ideas." "Three times during his

life he had an attack of an epileptic character, once in his seventeenth year after great exertion, one in his twenty-third year after sleepless nights *and one at the age of thirty years after influenza*. In this last attack he was carried home in a state of absolute unconsciousness."

An excellent illustration of this phenomenon is reported by Dr. William T. Shanahan in the communication above mentioned. Dr. Shanahan writes:

CASE 14.—"Althea D., aged twenty-three years, who developed epilepsy in infancy and had fairly frequent seizures for some time. She was admitted to the Craig Colony, July 30, 1908, and discharged January 5, 1909, as improved; readmitted December 21, 1911, and discharged January 8, 1915, as recovered, having had no seizures in over two years. In a communication had on July 22, 1919, from this former patient, she stated that subsequent to her discharge from the Colony she had no seizures until after a severe influenzal infection in November, 1918. Since this time she has had frequent attacks, as many as twenty in forty-eight hours in one instance."

Another very similar case of the reprecipitation of epilepsy by influenza occurred in our Boston series and will be presented here. These cases represent latent processes stimulated to renewed activity by the influenza neurotoxins.

CASE 15.—M. W., female, aged thirty-six years, Red Cross canteen worker.

Family History. Negative, except that she was three-eighths Hawaiian, and that a sister had epileptic seizures throughout her life and died at thirty-two after seven weeks of convulsions.

Past History. The patient was an intelligent and cultured woman whose past history was (aside from her epilepsy) simply that of an active and able school teacher. She had held some responsible pedagogic positions, and had travelled extensively.

Medically there was no point of particular interest aside from the present illness and the past epileptic attacks. Her habits were above reproach. Relatives and family physician were interviewed and a long history secured.

Epileptic History. Her first seizure was at the age of sixteen, *following a severe attack of measles*. Nothing further is remembered of this by any informant or the patient. The second attack was twelve years after the first, at the age of twenty-eight, the third two years later and the following year, at the age of thirty-one, she had a fourth attack. The present illness ushered in the next attacks, five years after the one just mentioned.

Present Illness. The patient had not been overwell for some months, partly owing, it was thought, to her supreme overexertion in the cause of the canteen work. One doctor said that she had "subacute appendicitis."

For about a week before admission she was definitely ill. She had had a fever of at least 102° at one time, three or four days prior to her admission, but in spite of feeling wretched and deserving to be in bed, she struggled on with her canteen work. There seems to have been little doubt but that she had influenza.

January 7, at 8.30 A.M., she suddenly had a severe convulsion, repeated at 2 P.M. and 4 P.M., and possibly one other time. She was unconscious after the first seizure: "Knew nobody and could not be taken care of."

Hospital Admission. The patient lay in bed when first seen and to all interrogations responded only with a hoarse groan, often reiterated. She suddenly jumped out of bed, uttering groan after groan, and danced about the room. The nurse led her to the toilet, but she ignored it. She continued her jumping and groaning. She could scarcely be held in bed, and when the nurse left her she crawled on top of the bed, removed her night-gown and squatted nude on her hands and knees, where she remained. Soon after this episode the patient began to clear up and within a few days seemed quite normal, although she was not wholly so for nearly a week.

Mental examination, aside from the points noted, physical examination, neurologic examination and laboratory findings were all negative.

Diagnosis: Series epilepticus, precipitated by influenza.

3. ALTERATION IN THE FORM OF THE ATTACKS. The only case illustrative of this phenomenon is one previously cited in a more general article referred to above and reprinted in abstract here. Noteworthy is the unusual change from the typical convulsive seizures to the somnambulistic or twilight state episodes as well as the increase in frequency of attacks. These cases illustrating the phenomenon of altering type of epileptiform manifestations are infrequent in the literature. I cite (free translations) two cases of Van Deventer's.¹⁶

A twenty-three-year-old male who, from the earliest youth until three years previously, had suffered from attacks of confusion (*Verworrenheit*) in which he undressed himself, ran hither and thither, as if seeking something, was brought to the hospital after an epileptic attack in the street, associated with influenza and urticaria. The day before he had felt ill, and as we learned later had had one attack which he himself did not remember. A week later he felt completely well.

A male patient of thirty-six, with slight facial asymmetry, who suffered occasionally from vertigo-epileptica and for the past twelve weeks also from headache, had, one morning before going to work, a severe epileptic attack. He regained consciousness first six hours later and seemed to be suffering with influenza associated with *tic douloureux*. He knew absolutely nothing of having had an attack, or that he had just come out of one. On the following day he was all right.

My own case now follows.

CASE 16.—Male, aged twenty-two years, single, discharged sailor, born in U. S. A.

Family History. Negative except that one paternal uncle is said to have had epilepsy.

Past History. Normal childhood. He left the high school and joined the U. S. Navy.

Medical History. Unimportant.

Epileptic History. Began at the age of twelve. Thereafter they occurred about every two months until about a few years prior to admission. The attacks entailed the characteristic tonic convulsions, frothing, biting the tongue, etc., but were not extremely severe, and as they were preceded by a somewhat prolonged aura he had never injured himself severely. They were always followed by a period of headache and malaise, with total amnesia for the events of the seizure. For a year or so prior to his enlistment in the navy they had been decreasing in frequency, under the treatment of Dr. Waterman, of Boston.

Present Illness. September 30 he contracted influenza and was in the hospital until November 1. He had pneumonia and was not expected to live. He was delirious during his acute illness and did not remember his father's visits. He had no epileptic attacks during the month (sic).

During November and December he had three attacks. These were of the nature of somnambulism, however, instead of the convulsive type as previously. He was noticed by his employer one day to be mismanaging his duties clumsily and when addressed did not reply, so was taken home where he subsequently recovered without memory for the event. Again, he suddenly left work, taking with him a friend's letter, to which he was in no way entitled, and was observed to stagger as if drunk. The third attack was the event leading to his coming to this hospital. He last recalls being at his work as usual; the police found him wandering the streets in an adjacent suburb of Boston, and, failing in satisfactory replies, he was brought by them here. "In the admission office he has to be prodded with questions frequently in order that any answers may be elicited, and to keep him awake. He said he could not tell where he had been living in Boston the past three years. Later replies that he was a radio student at Harvard."

He was taken to the ward, fell immediately asleep and when seen the following morning was quite clear, but could give no account of the interval between leaving work the day before and awaking in this hospital.

Mental examination, physical examination, and laboratory findings entirely negative. Psychometric test gave rating of 17 plus.

Diagnosis: Epilepsy; twilight state.

4. PRODUCTION OF A COMPLICATING PSYCHOSIS. The phenomenon of epileptic psychosis is only one of the recesses of that great mystery epilepsy. Analogous to the psychoses associated with hypophrenia, the psychoses associated with epilepsy are all too little understood. In both hypophrenia³⁵ and epilepsy, influenza evokes psychoses. In the following instances in every case the epilepsy was of long standing, yet all the stress and strain, haps and mishaps of life had not served to induce a psychotic episode. It surely bespeaks again for influenza the unenviable quality of a most potent neurotoxin.

Dr. O. S. Hubbard, superintendent of the Kansas State Hospital for Epileptics, kindly furnished the following case abstract:

CASE 17.—Mr. J., a clergyman, aged forty-four years, graduate of Boston University, had no family taint, but was a nervous individual. When four years of age received a head injury, and now has a small depression of the right motor area. About eight years ago, while sick with mumps, had "spasms of the left arm," since which time he has had occasional seizures, mostly petit mal, which were controlled to some extent with bromide. Was admitted here April 3.

About three weeks before this had influenza complicated with pneumonia. He seemed to be recovering from this attack when he developed an acute mania, was very restless, sleepless and noisy. Developed delusions directed against his wife and children, etc. Was controlled by drugs before entering the hospital, a considerable amount of morphin being used.

Upon entering the hospital he was noisy, talkative and did not sleep much. It was feared that he would die from exhaustion, but by careful feeding and attention to his general condition he gradually improved, and ultimately made a good recovery from his mania, and left the hospital in his usual state of mind. A letter from him states that he is feeling well and able to attend to some business affairs, but is not trying to do church work. This man had two Wassermann tests, which were reported as 2 plus and 3 plus.

In the case just cited the question of possible neurosyphilis is suggested and left unanswered.

In the following case, taken from our Boston series, there is obviously a combination of hypophrenia, epilepsy, influenza, parturieny and psychosis. Who will say how these should be placed as to cause and effect?

CASE 18.—Female, aged twenty-three years, born in Sweden, sixteen years in this country; married; housework.

Family History. This was quite meager. It was believed that her mother was a queer woman, with an exophthalmos, but not definitely psychotic, and no epileptic members of the family, direct or indirect, were known to her husband.

Past History. The patient was always a rather eccentric girl, but with a lovable, happy, sociable disposition, which made her popular in spite of her oddities. Supposedly following a fall "in childhood" (nothing more specific), she began to have convulsive seizures at intervals, persisting until puberty. They then ceased entirely and she is believed to have had none for nearly ten years. However, for some four years or more prior to the present account she had had what may be interpreted as psychic equivalents. "She will clear up for a time and then be peculiar again. . . . She makes simple-minded remarks. . . ."

October 2 the patient developed influenza and three days later was delivered of a seven months' pregnancy. From October 12 to 21 her temperature fluctuated from 97° to 99.5°. About October 20 she began to show mental symptoms. The chief of staff of the hospital wrote: "She now shows fear, anxiety, contriteness for supposed sins, wakefulness and loud calling at night. Wants to climb out of the hospital window, and says she hears and views strangers and has been very bad. Excited, depressed, nervous, feeble-minded (?)."

With this shower of psychic symptoms she began again to have epileptiform convulsions, having two on October 23 and at least one on October 24, the day of admission to the Psychopathic Hospital.

Mental Examination. When the patient was admitted she had a temperature of 101°, pulse of 110, respirations of 40. Examination of lungs confirmed a diagnosis of bronchopneumonia. Thorough mental examination was not practicable, but it was determined that she was approximately oriented, not grossly amnesic, but self-accusatory and deluded in vague and intangible ways. She preserved a fair insight, saying that she had had "influenza and a touch of pneumonia," her mind "mixed up," she was "seeing visions" and her "fits" were coming back, as in childhood, when she "falls down and bites" her tongue. She reacted to visual and auditory hallucinations; she heard the Kaiser outside her room and saw him "with a tail and all black." She was apprehensive and quite amenable to suggestions, obedient and not disorderly. She ate and slept well, kept herself covered and in bed, and was at no time violent.

Course. Her pneumonia signs disappeared by the end of a week and she is believed to have had but one more convulsion. There was at no time any muscular fibrillation, alteration of reflexes, diplopia, exophthalmos, etc., or other evidences of encephalitis.

She was up and about the ward after eight days and made herself agreeable and helpful. A routine mental examination was essentially negative except for absence of insight and a conspicuous defect in memory and intellectual processes, suggestive of hypophrenia. At times she was observed to laugh in a rather silly fashion and at other times to cry a little "for home, husband and family."

Physical examination in all ways negative, except as mentioned. Laboratory findings showed negative urine, blood serum, spinal fluid but positive smear for gonococci.

Psychometric rating was 10.7 on the Yerkes-Bridges point scale, with a variation total of 12. "In the supplementary tests her performance of the construction puzzles was good. She did poorly in the memory tests, adding details not in the original. She coöperated well and was interested."

She was discharged on the twenty-fifth day. The psychotic episode accompanying the convulsion may be interpreted either as a typical delirium, or, as seems better to me, as a transient epileptic psychosis. The basis of hypophrenia seems evident. The seizures are not likely to be regarded as encephalitic in the face of the facts that they preceded the frank pneumonia and were not accompanied by the more typical signs of encephalitis, and there is the history of epilepsy in childhood. The influence of the parturition is more likely to be overestimated than underestimated.

The following history is also from our Boston series, and is more typical of a "pure" epileptic psychosis:

CASE 19.—A. T., female, aged twenty-two years, Russian born, German descent: H. W. Admitted November 29, 1918.

Family History. The mother had had epileptic attacks "once every few years." No further data was secured except that she had not been psychotic. Otherwise the family history was irrelevant. Three normal siblings.

Past History. The patient was born in Russia and came to the United States at eighteen. She had always been a healthy child. She had four years of a common school education, and it is reputed that it was difficult for her to learn. She did some work on the farm in Russia, but housework only since arriving in America. "She is a good worker, but does not remain very long in one place, and usually found the work too hard."

Her personality is described as being "always good-natured, sociable and very happy; well liked by people, energetic, fond of dancing and very little of a reader." She used no alcohol, had no court record, was a Lutheran Church member and normally interested therein.

Present Illness. Epilepsy: Began to have epileptiform attacks in January, 1918. They were quite infrequent at first, and in fact there is no positive evidence that she ever had any more than the one first attack until after her influenza.

Influenza. The last of October she contracted influenza and was in the B. Hospital for three weeks. She then returned to her employer's home, but was not permitted to work on account of her physical weakness. November 23 she had a series of epileptic attacks (these are the words of the informant, and unfortunately

no further data was secured, except a corroboration by the patient of the occurrence of some seizures). She was in bed two days following this and incapacitated by weakness for two more days. November 28 "she began to forget things," showed queer conduct, disorder, said "flies kept her awake at night and that people were mean to her, that everyone was about to die, that the sun had gone down and hence her mother had died, everyone said their prayers and appointed her employer as her lawyer and delivered to him all of her small effects."

Hospital Admission. She was very noisy when first admitted, singing at the top of her voice as she marched about the ward gesticulating. The ideas that "race through her mind" were expressed in her endless loud singing, and she was quite inaccessible.

Mental Examination. The patient was totally disoriented in all spheres at times, although at other times gave correctly her name and address and once the date nearly correctly. After the first day she grew more quiet, was for a time depressed and then again disturbed. No delusions or hallucinations were proved. The attention was very poor, associations loose and slow, train of thought frequently broken and revealing irrelevancies. Her memory was notably defective for both recent and remote events.

Later the patient became apparently normal, so remained for a few days, and then became disturbed again within the week. A note reads:

"She is grunting and groaning in a monotonous, noisy way, 'Oh, Oh'-ing and 'Oh, my God'-ing with tireless repetition, not even stopping long enough to define her pains or answer questions. 'Here, there, help me, God! In my legs! Oh, my God! Oh, Oh, my arms! Oh, my legs and arms! Oh, my God! Oh, Oh!'"

Physical examination wholly negative, including gynecologic. Neurologic examination, including ophthalmoscopic, wholly negative, except for pseudoclonuses on the right side. Laboratory examination of blood, blood serum, spinal fluid and urine were negative.

Course. After ten days' observation she was committed to the Westborough State Hospital. I quote from a letter from the Superintendent, Dr. H. O. Spalding, regarding her condition on June 14, six months after commitment:

"We diagnosed her as a case of epilepsy. Wassermann negative. Orientation impaired. Train of thought confused and retarded. At times shows some spontaneity; emotionally unstable, apprehensive and worried. Hallucinations not established. Insight partial. She has improved some and goes to the industrial room daily and gets along well with the nurses and patients."

The following case from the writer's private practice may be briefly referred to here:

CASE 20.—A male, aged sixty-one years, developed epileptiform manifestations at the age of fifty-four. He was carefully studied by several neurologists, and the diagnosis of idiopathic epilepsy was made by exclusion. He had been having petit mal every few months and grand mal about twice a year, the last attack occurring in December, 1918, during the influenza epidemic. He did not, however, have influenza. Pneumonia of very severe grade in November, 1919, was followed by a postfebrile psychosis which was quite typical in its manifestations, gradually clearing and disappearing within a month. One seizure supervened.

III. EVIDENCE THAT INFLUENZA MAY CAUSE EPILEPSY.

Dr. L. Pierce Clark¹² recently presented in a brief report a case of influenza ushered in by epileptic attacks in a child of two years. The epileptiform seizures continued after the influenza, but were decreasing in frequency and severity. As Dr. Clark claims, this is the first similar case reported from the recent epidemic, but as I have pointed out,³¹ in previous epidemics the phenomenon has been noted repeatedly. Leichtenstern in his justly celebrated monograph¹³ writes:

" . . . Influenza frequently begins in children with an eclamptic seizure, and very rarely in adults with typical epileptiform attacks combined with total unconsciousness and succeed in stupor." He then goes on to consider "those cases in which directly following the influenza attack a typical but chronic epilepsy develops with seizures occurring in short or long intervals . . . (but) . . . so far as we know of these cases they all, after a longer or shorter time, end in recovery. We know of no recorded case in which permanent epilepsy followed influenza, although the occurrence is not thereby excluded. A case . . . of epilepsia gravissima may be mentioned here. . . ." He cites the case of a male of seventeen who began to have typical epileptiform seizures a few weeks after the termination of his influenza, which recurred with increasing frequency until ten to twenty-five attacks daily were experienced. Subsequently a distressing psychosis complicated, or at least dominated the picture, and he was committed, but eventually made a complete recovery.

Leichtenstern then goes on to discuss "many other forms of convulsions and disturbances in movement . . . observed during influenza or thereafter."

Gowers¹ cites 39 cases of epilepsy subsequent to scarlet fever, 12 to measles, 8 to typhoid and "a few" only to influenza. Voisin¹⁹ mentions influenza as producing epilepsy, but does not discuss it. Gelineau,²⁰ in his treatise on epilepsy, discusses the matter at some length. He concludes that influenza is "capable of giving birth to epilepsy or exercising over it influence of augmentation of number

and severity of attacks." He cites one case of his own: "An English girl, aged eight years, in whom there was apparently recovery following a ligation of the vertebral arteries." He cites 3 cases of Biet's,²¹ taken, he says, from Ulliel:

1. Jacksonian epilepsy in a physician of twenty-five with recovery.
2. A "young girl" with two epileptic grandparents who developed typical idiopathic epilepsy.
3. Jacksonian epilepsy in a male of forty-one.

He also refers to the cases of Kraepelin, Mariott and Bidon, and notes that some apparently were influenced favorably and some unfavorably.

Gelineau implies in his discussion that these epilepsies are probably manifestations of miliary cortical hemorrhages. This theory is the more plausible, it seems to the present writer, by virtue of the pathologic demonstrations of miliary hemorrhagic encephalitis in deaths from influenza or after influenza.

Other such cases of epileptiform attacks precipitated by influenza have been reported by Ruhemann,¹⁴ Landgräf,¹⁵ Van Deventer,¹⁶ and Jaccoud.^{17 18} Van Deventer¹⁶ cites 3 cases, which might be put in this group. One was an alcoholic male, forty-one, in whom influenza began by an epileptic seizure, followed shortly by another. The second was a man of forty, who, shortly after recovery from influenza, had a severe seizure while standing on the sidewalk. A twenty-two-year-old girl of good heredity, but herself peculiar, and excitable, had a typical epileptic attack at the onset of influenza. In all of these previous epileptic symptoms were denied.

Through the kindness of Prof. Adolph Meyer, of Johns Hopkins Medical School, the writer was permitted to see the following case, at the Phipps Psychiatric Clinic, in Baltimore, an abstract of which was graciously furnished.

CASE 21.—G., a farmer, aged thirty-five years, was admitted to the Phipps Psychiatric Hospital on January 9, 1920.

Family History. Entirely negative.

Personal History. Born in West Virginia. Measles and whooping-cough in childhood, otherwise quite healthy. He attended school in the country from six to eighteen years, finishing the eighth grade. He helped work his father's farm after school hours, and from the age of twenty-five he managed the farm alone with success. He was always an even tempered person with little tendency to disagree or argue. Never felt blue or restless. He was inclined to stay to himself; rarely mingled with girls. He had felt under obligations to support his family and was following the custom of the family to avoid marriage until late in life. There is history of autoeroticism from twelve to sixteen. Promiscuous sex relations until the present time, about once every few months.

Present Illness. In September, 1918, an attack of influenza kept the patient in bed for three weeks with headache, slight fever and extreme weakness, leaving him still weak and sluggish after convalescence. He undertook the usual duties about the farm in spite of his illness. In attacks coming about every other day he reeled as he walked and frequently had to support himself, and was weak and dizzy. He regained sufficient strength to finish jobs without serious handicap until the following summer, when he began to tire easily, and often was obliged to stop to rest. In August, 1919, there were periods of two or three minutes lapse of consciousness coming once or twice a week, when he suddenly stared into space or busied himself meaninglessly with queer undertakings; "mutters or walks about." At one time, while loading hay, he suddenly dropped the fork and wandered about the fields for three minutes without any recollection of the episode.

He has grown continuously weaker and nervous and more forgetful until he was obliged to stop work altogether in the fall of 1919 and January, 1920. He says: "I just lose my mind. It goes away so quick and comes back the same way. I do not know anything." Never falls or convulses. Brother says preceded by "swallowing."

Somatic Status: The patient presents no indication of systemic disorder other than hyperactive K. K. and A. J., fine tremor of the extended fingers and writing defect. Blood and urine negative. B. P., 124-76.

Mental Status and Course in the Hospital: Mental examination negative. While in the ward he has shown nothing in the way of abnormal behavior or attitude other than an occasional appearance of disinterest. Had seven attacks in January. Nine teeth extracted January 28. Three attacks subsequent week.*

The result of the questionnaire addressed to the superintendents of the hospitals for epileptics indicate that such cases were rare in the recent epidemic. Replies from Dr. O. S. Hubbard, superintendent of the Kansas State Hospital for Epileptics; Dr. H. B. Carriel, superintendent of Dixon (Illinois) State Hospital; Dr. A. S. Priddy, superintendent of the Virginia State Epileptic Colony of Madison Heights; Dr. David F. Weeks, superintendent of the Village for Epileptics at Skillman, New Jersey; Dr. L. V. Guthrie, superintendent of the Huntington State Hospital of West Virginia, and Dr. T. B. Bass, superintendent of the State Epileptic Colony of Abilene, Texas, make a unanimous reply in the negative

* In the hospital he had two attacks of lapses of consciousness. On January 14, 1919, he sprang from his bed; brushed the nurse aside and stalked down the corridor to return immediately in full consciousness without recollection of doing anything out of the way. On the 15th he sat quietly in a chair and mumbled in an undertone several times "get 'em out of here" and made brushing movements with the hands. He then took the bed clothes off the chair, turned the mattress down on another bed and was about to crawl into it when he came to himself. He has never had convulsions, tongue biting, incontinence, or falling spells.

to the question as to the number of cases admitted in which epilepsy was given or considered as a precipitating factor.

One further case is, however, reported by Dr. W. T. Shanahan, of Craig Colony.

CASE 22.—J. O'D., male, aged nineteen years.

Family History. Mother died at forty-four years of influenza. Father living and well, aged forty-two years, a barber, for twenty-five years markedly alcoholic.

Patient is the sixth in line of birth of ten living children. Three girls died in infancy. No history of nervous or mental disorders in family.

Past History. Patient born October 17, 1900; apparently normal birth, nursed by mother. History of convulsions during dentition. No difficulty in learning to walk or talk. Alleged to have had infantile paralysis at two years, followed by hemiplegia. Began school at six years, graduated from public school at fifteen years and attended night school for one year. Had measles at three years, diphtheria at twelve years.

Present Illness. Had severe attack of influenza during the fall of 1918. Following this he had a severe convulsion. His convulsions recurred daily for a short time, when he was free for three or four weeks. After admission to the colony he had a typical grand mal seizure, apparently no aura. Seizures occur both during sleep and waking periods.

At time of admission to the colony he was dirty, and apparently had given no attention to personal cleanliness. Features small, with eyes set close together. Ears small and close to head. Nose narrow and pointed. Many carious teeth, some missing. Palate narrow and high arched. Heart, lungs and abdomen negative. Marked right lateral curvature of spine, compensatory for shortening of the right leg. Flaccid paralysis of right lower extremity with extreme atrophy of muscle. Right thigh circumference, 11 inches; left thigh, 17½ inches; right calf, 7½ inches; left calf, 13 inches; right ankle, 6 inches; left ankle, 8 inches. All reflexes normal except right lower extremity. No Babinski.

Mental Examination: Scored fifty-four points with Yerkes-Bridges point scale. Would not coöperate in various tests.

What attitude shall we take toward these cases of apparent epilepsy which were precipitated by influenza? Shall we turn to Gelineau's attractive theory of miliary cortical hemorrhages as the result of influenza and the cause of epilepsy? All of us have seen cases of cerebral concussion followed by epileptiform attacks* and

* Dr. W. F. Bowen, Topeka, gave me the details of the following case: A boy of sixteen was struck in the head with a batted baseball. He walked to the bleachers and sat down holding his head in his hands for a few minutes and then tried to resume play. About an hour later he fell to the ground unconscious. He was unconscious

it has been demonstrated by McCallum²⁹ and other pathologists that one of the primary lesions of influenza toxin is an endothelolytic production of multiple hemorrhages. We have shown¹¹ that this occurs in the brain as well as elsewhere, and may produce symptoms. Now the question arises as to whether these cases reported may not be those so produced, and if so whether or not they are to be regarded as essential idiopathic epilepsy. Of course, the question perhaps hinges altogether on the meaning and delimitation of the word epilepsy.

The opinions of Dr. E. E. Southard, Dr. Adolph Meyer, Dr. S. E. Jelliffe, Dr. Wm. S. Shanahan and Dr. L. Pierce Clark were solicited as representative of the schools of thought concerning epilepsy in this country. The lamented Southard had given me his idea orally and was to have put it in writing the week of his untimely death. That he probably would have taken the view of an organic causation, *i. e.*, "epileptogenic foci and perhaps tissues favorable to epileptic discharge,"²¹ for most syndromes which we call epilepsy, whether produced by an influenzal encephalitis, a syphilitic encephalitis or an idiopathic encephalitis, is apparent from such studies as those done in association with Lucas in 1912,³⁰ and alone in 1908.²⁴ The opinions of the other men follow:

Dr. Jelliffe writes:*

"That influenza can produce not only somatic interruption of energy distributing pathways by exudative phenomena or abscess formation, or other typical encephalitic process, is obvious. That such interruptions can result in the epileptic discharge is also obvious and well documented. My own experience has scores of cases and the literature is abundant.

"Furthermore, that reduction in resistance, general functional lowering of distribution capacity, *a la Janet's* 'Niveau Mentale,' can permit the specific reactions called epilepsies to come through is also to me obvious, without any microscopic cellular alterations. Microscopic or chemical alterations with energy carrying capacity reduction lie behind these. These are, I think, equally obvious.

"The whole body as a distributing organism—effectors in their totality—can be seriously hampered by the interference in the coördinating pathways. I see no reason why we should not call them epilepsies if we are fairly definite as to what we can agree upon as to what is subsumed under the symbol. My own notion regarding the nosology is purely pragmatic and I am rather a little dubious as to the prevailing absolutistic nosologic entities."

for twenty-four hours and at that time an exploratory craniotomy was decided upon. The brain was exposed and no single large bleeding discharge was found as expected, but the entire surface of the brain exposed was studded with minute focal hemorrhages. The skull and scalp were closed and the lad made an uneventful recovery, but thereafter suffered from typical attacks of epilepsy. The skull was reopened by other surgeons repeatedly in attempts to remove some point of irritation but without avail.

* From a letter of January 15, 1920.

Dr. Adolph Meyer writes (June 16, 1920):

"I can give you my general conception of the relation of epilepsy and infectious diseases. A large number of infectious febrile disorders and toxic disorders tend to lead to deliria and to convulsions. I am in the habit of connecting deliria with conditions which show also through the presence of edema of the membranes and perhaps also of the brain itself. This same condition is observed in epilepsy. To what extent miliary hemorrhages play a specific role in the production of epilepsy I would not be able to say. I do not, however, consider them essential and specific. In the main I would say it is probable that any cortical damage, either by poison or other injury including arteriosclerosis and circulatory disorders, can be the potential foundation for epileptic attacks.

"I may say that I am very much surprised to see so few of the encephalitis cases of the present epidemic with epileptic attacks. For the role of influenza it might be of value to inquire whether the cases that later developed epilepsy showed any special tendency to delirium or any cerebral involvement during the attack."

Dr. Clark writes:

"As regards the epileptic sequelæ of influenza, I am quite well aware of the fact that the Spanish influenza did aggravate in many instances epilepsies previously existing and in some instances seemed to have renewed attacks in those previously in a state of epileptic arrest.

"I think your criticism was quite true, that the boy was probably predisposed to epilepsy in his backwardness of mental development and probably possessed an irritable and sensitive nervous system upon which the influenza seemed to have acted as a precipitating factor for the attacks. In view of these facts one must say that probably the case is not one of essential epilepsy but rather epileptiform and symptomatic in character and probably the prognosis will be very sound in such a case. But this, I think, only goes to prove that the influenza was really an initiator of the disorder and that it would probably not have been in evidence had it not been for the influenza.

"Singularly enough, Dr. Jelliffe thought also that my article concerned itself with influenza in general, and he believes that the present epidemic is not so dissimilar from ordinary influenza, to which I take great exception, after having seen a good deal of it both in clinics and in my own home. The bibliographic references that you gave to the old forms of influenza are quite pertinent to the disorder as we formerly knew it."

Dr. Shanahan writes (abridged from letter of January, 1920):

"I believe that after influenza, or any other severe infection which, during its course, attacks the central nervous system and damages the organic structure so that permanent change results, one may expect not only a mental deterioration but also some of the phe-

nomena ordinarily called epileptic. Again, of course, there may be but temporary disturbance of function of the brain or other organs of the body having control directly or indirectly of brain functioning, *i. e.*, endocrine glands, etc., and, as a result, epileptiform seizures.

"The degree of keenness of observation, the individual equation, the differing viewpoints, the varying severity of the influenza, the different sections of the country or world, the different years or epidemics, must all be considered. In the earlier epidemics classed as influenzal in nature how many looked for symptoms epileptiform in character?

"Personally I feel, as do many others, that the cause of influenza, be it bacterial or something else, makes itself apparent every winter or at least practically so, varying in intensity.

"In the winter of 1915-1916 we had at the colony a considerable number of cases of what was then called influenza. Several adults had marked delirium, twitching, etc. In some young patients, some not epileptic, there was apparently an encephalitis from the symptoms presented. A boy of four years, who was very fair mentally, developed in January, 1916, a severe illness which after a short time resulted fatally. He had had during practically a year preceding no seizures. With the onset of the illness referred to he had a series of severe convulsions with pulmonary edema, following which he continued in a stupor, practically a coma, occasionally crying out. A right hemiplegia developed. Until death, he had frequently convulsive movements confined to part of the right side and then again on the left side, but no further general convulsions. Lumbar punctures gave a clear fluid with no increase in cell count. He presented a double Babinski and exaggerated reflexes on the right side, pupils reacted normally to light, both fundi congested, right disk slightly blurred. Increased pressure observed when lumbar puncture was made on the seventh day of illness. On the ninth day of illness paralysis of the right side was less marked. No evidence of pneumonia. Babinski still present on both sides. Pupils react to light; no strabismus, but a lateral nystagmus was observed at times. On the eleventh day the patient died, apparently of a terminal pulmonary edema. Diagnosis was *encephalitis following influenzal infection*. Autopsy showed tremendous edema of the brain, so that the surface was misshapen, the convolutions being crowded together so that the sulci were only represented by lines. There was recent hemorrhage on the right side of the cerebellum. Unfortunately a microscopic examination of the brain could not be made.

"In November, 1918, during the influenza epidemic, Harry L. R., aged thirty-one years, who had long been a patient at the colony and was subject to frequent periods of mental excitement, developed a severe influenza, with jaundice and high temperature, dying on the eleventh day. Autopsy performed an hour and a half

after death showed the meninges considerably thickened and very cloudy and of the extreme yellow color. There was some hydrops of the subarachnoid space. The yellow discoloration did not extend into the brain substance. The brain itself was firm without gross lesion. Apparently the edema was not as marked as in the other case cited.

"I mention these two cases as a proof of similar infection during two periods and as evidence that extensive involvement of the brain and its membranes occur, and as a result such permanent structural damage takes place as to bring about disturbance of function, so that it would be very possible for the symptoms of an epilepsy to appear, even in an individual not epileptic."

IV. "THE INFLUENCE OF EPILEPSY UPON INFLUENZA."

This phrase is of French extraction, being taken bodily from the title of Maillard and Brune's article cited above.¹⁰ Their observation that epileptics were unusually susceptible to influenza was supported by experience in this country. Without entering into the subject in detail we may cite as representative testimony the report of the manager of the State Epileptic Village at Skillman, New Jersey.

"When the first case of influenza occurred the population of the village was 900. There was 422 cases of influenza, with 67 deaths. . . . More than 46 per cent. of the entire population contracted the disease, the case incidence being substantially higher among the epileptic patients than among the employees; 48.9 per cent. in the former against 34.8 per cent. in the latter."

Summary. It appears, then, that insufficient attention has been paid to the influence of influenza, or, for that matter, of any of the acute infections, upon idiopathic epilepsy. Little reference to it can be found in the literature. Such fragmentary treatment as the subject receives here and there is inconclusive. The beneficial effect of acute infections, at least in so far as they inhibit epileptic attacks during the febrile period, is insisted upon by probably the majority of those considering the matter at all. One writer inclines toward a sort of specific differentiation, concluding that this infection increases, this one decreases epileptic manifestations. A few writers are convinced that infections benefit epilepsy permanently, and one even suggests exposure to pneumonia as a possible cure for a preëxistent epilepsy. But nearly all of these writers are strangely silent about the most ubiquitous of all modern epidemic infections, influenza.

For this optimistic impression of the effect of influenza upon epilepsy we find some little support from the recent pandemic. Questionnaires addressed to the superintendents of state hospitals

for epileptics were graciously answered. From these, and from data accumulated at the Boston Psychopathic Hospital and a few other sources, evidence of inhibition of attacks during the febrile period, and of decrease in frequency and perhaps severity of attacks following influenza, was secured. Illustrative figures and cases are cited.

On the contrary, however, we also have evidence, secured from the same sources, that the effect of influenza upon epilepsy may be and probably more often is aggravation. This, it appears, may be demonstrated by a simple increase in the frequency, if not in the severity, of the attacks; it may occur as an alteration in the form of the epileptic attacks; or it may appear in the production of a complicating psychosis. All of these unhappy equations are illustrated above by cases. Statistics would indicate that these deleterious effects of influenza were distinctly more frequent than the beneficial effects.

Nor is the obverse side of the picture yet complete. It appears that an epilepsy, previously manifested but long latent, may be fanned into flame again by influenza, and finally that epilepsy may perhaps be primarily caused by influenza in previously healthy persons. Numerous cases of epileptiform seizures occurring for a while after influenza, but usually ceasing, never to recur, have been reported in past epidemics. From the recent epidemic 3 cases are presented. Various opinions are held as to the significance of this phenomenon.

Of the four actions of influenza upon mental disease, which previous studies have led us to conclude are the usual ones, namely, creation, precipitation, aggravation and amelioration, all are represented in the case of epilepsy. As to "creation" some might quibble, but I believe we are pragmatically justified in assuming that the cases reported by Leichtenstern, Landgraf, Ruhemann, Van Deventer, Jaccoud, Clark, Shanahan and others really represent "epilepsy" produced by influenza, albeit epilepsy with a good prognosis, and, of course, not "idiopathic" epilepsy. We are scarcely justified in rejecting what is apparently typical epilepsy merely because the adjective "idiopathic" is no longer strictly applicable or the termination the conventional one. Presumably they are the product of influenzal neurotoxins and a susceptible brain. The fact that they are apparently reversible in reaction may as well be imputed to a peculiarity in the combination; presumably it is dependent on the type of effector (neurotoxin) rather than the type of receptor (neuron). Reversible reactions are not unfamiliar in the case of other diseases usually regarded as permanent, *e. g.*, Schizophrenia.²²

Finally, the effect of epilepsy on influenza is the production of a generally lowered resistance, and hence abnormally high morbidity and mortality rates as compared with normal patients.

Conclusions. From a study of pertinent literature and of clinical material afforded by the epidemic of influenza of 1918-1919 the interrelations of influenza and epilepsy may be summarized, in conclusion, as follows:

1. The effect of influenza upon idiopathic epilepsy is not uniform.
2. Beneficial influence is occasionally observed; seizures are perhaps usually absent during the febrile state and in some instances occur with decreased frequency after the acute infection. There are no cases on record in which influenza has induced an entire cessation of epileptic attacks once instituted.
3. Deleterious influence is more frequently observed. This is manifested in various ways.
4. Seizures may occur with increased frequency following influenza, both as compared with short periods and long periods of time prior to the acute infection.
5. The character or type of the seizures may change subsequent to the influenza, in addition to or independent of the increase in frequency.
6. Epilepsies whose manifestations have long lain latent may be incited to renewed activity by the attack of influenza.
7. Psychoses may be precipitated in epileptics by influenza, as in non-epileptics.
8. Epileptiform syndromes which resemble typical idiopathic epilepsy, except that recovery usually occurs shortly, are occasionally evoked by influenza. Probably we should regard these as recoverable or "reversible" types of idiopathic epilepsy, the product of influenza and a (possibly) susceptible brain. Possibly they are manifestations of multiple miliary (encephalitic) hemorrhages.
9. But the majority of epileptic patients who had influenza did not exhibit any alteration in their disease.
10. The effect of "epilepsy on influenza" was observed to be a lowered resistance, and hence increased morbidity and mortality rates (as compared with normal persons).
11. Influenza thus appears to exhibit, in the case of epilepsy, the properties previously demonstrated to be operative in the case of the psychoses associated with influenza: creation, precipitation, aggravation and amelioration.

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REVIEWS.

A TEXT-BOOK OF THE PRACTICE OF MEDICINE. By JAMES M. ANDERS, M.D., PH.D., LL.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania; Consultant Physician to the Jewish Hospital and to the Widener Home for Crippled Children; Officier de l'Instruction Publique. Thoroughly Revised, with the Assistance of JOHN H. MUSSER, JR., B.S., M.D., Asst: Professor of Medicine, University of Penna.; Physician to the Philadelphia General Hospital; Physician in Charge of the Medical Dispensary, University of Pennsylvania; Assistant Physician and Chief of Dispensary, Presbyterian Hospital. Pp. 1284; fully illustrated. Philadelphia and London: W. B. Saunders Company.

THE previous thirteenth edition of this standard work on medicine had received such a thorough overhauling that we did not think that much could well be done to it in the way of omission, addition or revision. Since this former edition, of course, we have participated in a war and many things have been learned and experienced in the domain of internal medicine. The references and text of this new fourteenth edition give abundant proof that the authors have been on the alert and have conscientiously given the reader the important new material as it has appeared in the literature since the 1917 edition. It would be interesting to discuss the text of the changes as they have been made, but the limitations placed on this review do not permit it.

The section on typhoid fever has been somewhat abridged. The sections on typhus fever, yellow fever, cerebrospinal meningitis, pneumonia, icterohemorrhagic spirochetosis, diabetes mellitus, scurvy, pellagra, pernicious anemia, exophthalmic goiter, focal infection, tuberculosis, mumps, measles, hemolytic jaundice, hemolytic anemia of pregnancy and the puerperium have been well amplified. The subject-material covering hay fever and asthma has been much improved by incorporating further studies of these disorders in their relation to foreign protein.

The chapter on influenza has been rewritten, especially including findings gleaned during the recent pandemic.

New subject-headings include bronchial spirochetosis, streptococcic (hemolytic) pneumonia, trench nephritis, disordered action of the heart, chronic (syphilitic) aortitis, interstitial emphysema

epidemic encephalitis, oxycephaly, methyl alcohol poisoning and botulism.

The arrangement of the book remains, as it has always been, extremely satisfactory. For the student and practitioner it is a good, concise work on the broad field of medicine. The present edition has incorporated in its lines the most recent contributions from the literature, making it a volume well worth while.

T. G. S.

THE ROENTGEN DIAGNOSIS OF DISEASES OF THE ALIMENTARY CANAL. By RUSSEL D. CARMAN, M.D., Head of Section of Roentgenology in the Division of Medicine, Mayo Clinic, and Professor of Roentgenology (Mayo Foundation), Graduate School of Medicine, University of Minnesota. Second edition. thoroughly revised. Pp. 676; 626 original illustrations. Philadelphia and London: W. B. Saunders Company.

IN the second edition of this well-written and very readable book the author gives to the profession at work that stands out preëminently among its kind. It has been brought up to date by a revision of the text and the addition of two new chapters—one on hour-glass stomach and the other a chronological abstract of the published work on pneumoperitoneal diagnosis.

While the author has drawn freely on the experience of other workers in like fields, his book, with the exception of the chapter on pneumoperitoneal diagnosis, is largely the result of his own indefatigable efforts. His deductions are based on the observation of many thousands of cases examined by himself and seeing his results checked up at the operating table or in the autopsy room.

The principal feature which distinguishes the second from the first edition is the chapter on hour-glass stomach. This chapter is done with the same thoroughness that characterizes the work on the other chapters. Congenital, acquired and pseudo-hour-glass contractions are discussed, with particular emphasis, on the differentiation of the organic from the spasmodic form of the acquired variety. The chapter on pneumoperitoneum is a reflection of the work done by other investigators, with a description of the technic and a timely warning as to the dangers and complications of this procedure. What the author thinks of it is best told in his own words. "If the patients are carefully chosen pneumoperitoneum should prove a valuable aid to diagnosis, but it should be resorted to only after all other methods of examination have failed."

Distinguishing features of the book are the very good illustrations and complete case reports. It can be heartily recommended as a text-book for the roentgenologist, be his experience large or small.

J. D. Z.

SURGERY OF THE LUNG AND PLEURA. By H. MORRISTON DAVIES, M.A., M.D., M.C. (CANTAB.), F.R.C.S. (ENG.), Hon. Captain, R.A.M.C. (T.), Consulting Surgeon, University College Hospital; Consulting Surgeon, City of London Hospital for Diseases of the Chest; Medical Superintendent, Vale of Clwyd Sanatorium. Pp. 259. New York: Paul Hoeber.

THERE is no doubt a place in our literature for a work dealing with the above subject. It comes close on the heels of several of the very excellent contributions, but written as it is in such an easy and simple style it will no doubt receive a warm reception. Thoracic surgery has improved so remarkably in its ramifications and its technic that we should welcome Davies's experience. The anatomy of the chest is minutely discussed, especially as regards surgical anatomy. The illustrations in this chapter do not do justice to the work either in clearness or in numbers. Intrapleural pressures are discussed in several intensely interesting pages. It is to be regretted that the author does not refer to the vast amount of literature which Evarts Graham has contributed to this subject. The chief shortcoming of the book is the terseness with which empyema is discussed. Barely thirteen pages are devoted to this most important subject. The author differs in his conception of the treatment of streptococcic and pneumococcic empyemas from the view held here in America. Setting up exercises and high caloric feeding in the postoperative management of these cases is not even mentioned. The most valuable portion of the book is the minute description of the surgery of tuberculosis. The subject is extensively discussed, especially as regards nitrogen displacement in various pulmonary tuberculous pathologies and complications. This chapter is the author's best contribution, and it alone will fully compensate the reader of the book. The roentgen-ray pictures are numerous and clear. They show contrasts and hilus pictures with an exactness not often to be found in text-books.

I. S. R.

A LABORATORY MANUAL AND TEXT-BOOK OF EMBRYOLOGY. By CHARLES WILLIAM PRENTISS, Late Professor of Microscopic Anatomy, Northwestern University Medical School, Chicago. Revised and Rewritten by LESLIE BRAINERD AREY, Professor of Microscopic Anatomy at the Northwestern University Medical School. Third edition, enlarged. Pp. 391; 388 illustrations, many in colors. Philadelphia and London: W. B. Saunders Company.

THE fundamental importance of a thorough knowledge of the stages by which the organs of men have reached their adult develop-

ment becomes more and more apparent to abdominal surgeons and other specialists as cases of anomalous formations and congenital malformations of various structures are met and studied. Considered from a purely scientific aspect, obstetrics is essentially but applied embryology. To the student, embryology is in itself, perhaps, a dry and quickly forgotten subject; but the contrasting of the evolution of the human organs with those of other vertebrates and the relation of these steps to the gross anatomy of the organs, as is done in this volume, brings out a new interest. To these two classes, students and practitioners, the present volume must appeal. The book is well printed, the illustrations not too complex, well executed, and the book is enhanced by many colored plates.

The subject-matter is divided into various chapters devoted to studies of the germ cells, the germ layer, chick, human and pig embryos and their dissections. The various basic systems of the body are then taken up and fully described as to the various changes and modifications which occur in them during their development to adult organs.

That the book has gone through three editions in five years is a token of its value and of its appreciation by the medical profession.

P. F. W.

NERVOUS AND MENTAL DISEASES. By ARCHIBALD CHURCH, M.D., Professor of Nervous and Mental Diseases in the Northwestern University Medical School, Chicago, and FREDERICK PETERSON, M.D., formerly Professor of Psychiatry, Columbia University. Ninth edition, revised. Pp. 949; 350 illustrations. Philadelphia and London: W. B. Saunders Company.

THE ninth edition of this work on *Nervous and Mental Diseases* by Church and Peterson shows little radical change from the edition published in 1915.

The book is divided, as heretofore, into two separate treatises. The first is by Church and deals with nervous diseases, while the second, by Peterson, is devoted exclusively to mental disorders.

It is interesting to note in both sections that only passing reference is paid to the theories and studies of Freud. The authors remark: "Some radical views which have attained considerable popularity have not been incorporated, more time and experience being thought requisite for their unquestioned establishment." Likewise only scant treatment is given to the field of the war neuroses, concerning which so much has been recently in print.

The only chapters which show any active reconstruction are those on general paralysis of the insane and traumatic insanity, these being elaborated and corrected in view of the advances made in the etiology and treatment of these disorders.

The book is an excellent text on the subject for general practitioners, and especially for students, as it is conservative and concise, and all the subjects are presented in a systematic and interesting manner. The new edition will undoubtedly continue the excellent reputation of its predecessors.

F. H. L.

SLEEP-WALKING AND MOON-WALKING. A MEDICO-LITERARY STUDY. By DR. J. SODGER, Vienna. Translated by LOUISE BRINK. From the Nervous and Mental Disease Monograph Series, No. 31. Pp. 138. New York and Washington.

THIS psychoanalytic monograph is perhaps best described by quoting from the first and the last chapters of the edition.

"Psychoanalysis holds a key to the problem of sleep-walking, which alone has been able to unlock the mysteries of its causes and its significance. This key is the principle of wish fulfilment."

"Sleep-walking under or without the influence of the moon represents a motor outbreak of the unconscious, and serves, like the dream, the fulfilment of secret forbidden wishes, first of the present, behind which, however, infantile wishes regularly hide. Both prove themselves in all the cases analyzed more or less completely of a sexual erotic nature."

The above phrases describe the monograph *in toto*.

F. H. L.

DISEASES OF THE EAR. By PHILIP D. KERRISON, M.D., Aural Surgeon to the Willard Parker Hospital for Infectious Diseases. Second edition. Pp. 596; 333 illustrations. Philadelphia: J. B. Lippincott Company, 1921.

THE second edition of Kerrison's book fully conforms to the high standard set by the previous edition and should continue its popularity. The arrangement of the subject-matter is unique, and, on the whole, praiseworthy, making for ease of reference while adding to the conciseness and attractiveness of the text. The cuts are original and well drawn, admirably illustrating the subject-matter. Naturally, from the nature of the case, most of them are anatomical and give the student new and often illuminating ideas as to the topographical anatomy of the temporal bone in its relation to aural function and operative procedures. New chapters have been added and old ones amplified to include the latest developments in aural research and technic. Such, for instance, is the comment on postoperative tissue repair in mastoid surgery, and the resultant modification in postoperative technic

in the closure and treatment of the mastoid wound, resulting in quicker and more satisfactory results in healing. The result of the study of the cerebrospinal fluid in various diseases is given and its influence in correcting errors of diagnosis in meningeal lesions and disorders of otitic origin is interpreted. The first edition devoted considerably more space to the labyrinth in disease and the various tests of its function than most text-books on otology. This work is now carried forward by the addition of a short chapter on Bárány's theory of cerebellar localization, a subject very much before the otological and neurological branches of the profession at the present time.

The volume is a complete work on ear diseases and gives the reader a most satisfactory and up-to-date review of the subject as well as a definite and detailed guide to the various therapeutical and surgical procedures indicated in different aural conditions.

G. M. C.

VENEREAL DISEASES. THEIR CLINICAL ASPECT AND TREATMENT.

By J. E. R. McDONAGH, F.R.C.S., London Lock Hospital.

First edition. Pp. 403; 127 illustrations (106 in color). St.

Louis: C. V. Mosby Company.

THE following statements are to be found in this volume on venereal diseases.

Page 5: "As the following pages will indicate, I believe that the *Spirocheta pallida* is only the adult male of a coccidial protoöön . . . As proofs for these views are beyond the scope of this, a clinical volume, and as the work is being confirmed, a special pathological volume will be published as soon as possible."

Page 13: "There is only one certain way of diagnosing a sore, and that is by looking at it."

Page 16: "If a patient has a sore or sores on the skin of his penis the chances are 90 to 1 that they are syphilitic."

Page 14: "Connective-tissue cells can proliferate more abundantly in some areas than in others; moreover, there are areas in which, even if the connective-tissue cells did proliferate abundantly, it would be difficult to feel them."

Page 32: "The distribution of the blood supply in the skin is not unlike that in the liver, *i. e.*, the skin is divided into circular areas roughly about the size of a shilling. . . . In the center of each circular area an artery runs. . . . It is along this central artery that the organisms reach the skin and it is in the walls of vessels that the organisms develop. . . . Occlusion of the lumen would result in the loss of blood supply to the circular area affected; consequently, the skin corresponding to this area would necrose, an ulcer would be formed, or, in other words, a gumma."

Page 42: "Syphilitic lymphatic glands are hard and discrete, or enlarged, matted together and soft."

Page 274: "The gonococcus is not necessarily a pus-producing organism; note how comparatively infrequently gonorrheal complications are associated with pus formation."

Page 276: "It is probably owing to their difference of tissue in the two parts of the canal that strictures are most apt to develop in the posterior part of the urethra."

Page 296: "If the gland is enormously enlarged and painful and the two lobes cannot be differentiated the patient if under fifty years of age has a prostatic abscess."

Page 297 (speaking of prostatic comma shreds): "Their presence usually denotes that the patient is either neurasthenic or has been overtreated."

Page 298 (speaking of complete urinary retention in acute posterior gonorrheal urethritis): "In no condition is the effect of colloidal manganese more marked, because one injection will rid the patient of the subjective symptoms and enable him to pass his urine without assistance."

Page 387: "It is my object, therefore, in this chapter to attempt to show the relationship between syphilis and other diseases; but particularly between the symptoms produced by it and well-known poisons, and the role it plays in the etiology of malignant disease."

Anyone subscribing to these tenets will be interested in possessing this book.

A. R.

THE STORY OF THE AMERICAN RED CROSS IN ITALY. By CHARLES M. BAKEWELL. Pp. 208; 21 illustrations. New York: The Macmillan Company.

AN account of the American Red Cross activities in behalf of the Italian army, of the American soldiers who served in Italy, and of the suffering population throughout the country during and after the World War, is interwoven with observations on the political situation, war history and descriptive passages. Emphasis is laid on the improved morale of the Italian people and the better feeling toward America due directly to Red Cross relief work. Many grateful expressions from Italians are cited. Chapters entitled "A Tour through Italy in the Wake of the Red Cross" comment on conditions in principal Italian cities and resemble a guide book in pointing out interesting places. The fight against tuberculosis and the organized continuation of the work through the League of Red Cross Societies are featured in the conclusion. There are maps, pictures, and appendices giving an account to expenditures and list of personnel.

T. G. M.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Uremia, (Harvey Lecture, 1920.) — FOSTER (*Jour. Am. Med. Assn.*, 1921, lxxvi, 281) says our present-day conception of uremia is reviewed and summarized. It is noted that uremia is an intoxication which may occur in nephritis and which manifests itself by psychomotor disturbances. The symptoms may be roughly divided into three groups: (1) Toxic: headache, vomiting, diarrhea, amaurosis; (2) psychic: hallucinatory paranoid states, stupor and coma; (3) motor: transient paralyses, paresis and hemiplegia and convulsions. Dependent upon the occurrence of these symptoms in a given case clinical types of uremia are recognized: (1) Convulsive or epileptiform type. Initiated by headache and sudden amaurosis (the latter without demonstrable lesions in the eye), a convulsion occurs. Coma is a sequel. The convulsive seizures and the not infrequent recovery are striking features. (2) A second type characterized by gradually deepening coma without psychic or motor disturbances. (3) A third type in which lethargy and somnolence occur along with gastro-intestinal and psychic disorders. Visual disturbances occur, as a rule, only in the presence of demonstrable retinal changes (hemorrhages, exudate, neuritis). Convulsions are absent. Edema of the brain in connection with uremia is discussed and the author finds that "in its highest severity it occurs with constancy in but one type of uremia, that type in which stupor and coma without convulsion, without psychic or motor disorders, is the prominent nervous symptom." Definite cerebral hyperemia, with or without slight edema, he has observed in only one group of cases, viz., that in which the subject had died of the convulsive type of uremia. Having

previously noted that, anatomically, "aside from the lesions in the kidney and occasionally ulceration in the gastro-intestinal tract uremia leaves but few signs," and having discussed the cerebral condition frequently found in association with certain types of the condition, the author considers uremia from the standpoint of an intoxication. Anuria (as a result of ureteral obstruction, ligation of renal arteries, bilateral nephrectomy, etc.) is discussed and the symptoms resulting from it differentiated from those occurring in epileptiform uremia. Other differences are pointed out: The retention of water in the case of the anuria with the resulting dilution in the body of the retained nitrogenous substances; in anuria all the substances normally excreted in the body are held back while in nephritis some are retained more than others. It is pointed out that uremia may not be only a consequence of water loss through the kidneys but may also follow diaphoresis or restriction of the fluid intake. In connection with his discussion of the blood chemistry of uremia the author states that it seems definite that the tissues retain more of the nitrogenous bodies than does the blood and that there is some ground for the belief that the excess of these bodies in the blood is simply an expression of the supersaturation of the tissues. The sharp, clinical contrast between the convulsive and asthenic types of uremia is emphasized. Feeling that if the former is an intoxication the toxin should be recoverable from the blood or tissues the author attempted the isolation of various organic substances from the blood of patients suffering from convulsive uremia in order to study their effect on animals. Colloidal methods such as used for the separation of alkaloidal bases were employed and the base recovered in a pure state for the tests. The solution of the base from the blood of 22 cases of convulsive uremia, and from twice that number of controls, was injected intraperitoneally into guinea-pigs. In the case of the former uniformly fatal results were obtained. Polypnea, muscular twitching, convulsive seizures and death within a few minutes was the usual occurrence. In some experiments paresis of the hind legs and diarrhea preceded the convulsions. In a few convulsions were absent, death being preceded by twitching movements and a stuporous condition. No toxic substance was isolated from the blood of control patients. The substance isolated is basic in its properties and forms crystalline salts with platinum and gold. Nothing is known of its chemical nature because of the inability to collect a sufficient quantity for analysis. Although the author states that "the existence of a toxin in uremic blood will not have been demonstrated until its chemical identity is known," he feels that his investigations "seem to indicate that the blood of patients with epileptiform uremia contains an organic base which is toxic."

A Study of the Spinal Fluid in 1869 Cases of Syphilis in All Stages.—WILE and MARSHALL (*Arch. Dermatol. and Syphil.*, 1921, iii, 293). Based on a study of these cases the authors conclude: (1) The nervous system, if uninvolved as shown by the accepted criteria during the first months of the infection, is seldom involved later. A negative preliminary puncture followed by positive findings at a later date occurred in only three of several thousand cases punctured. (2) Of the several criteria indicating involvement, the increase of organic solids

is found to be slightly higher than either the cell count or Wassermann reaction, the relative value being indicated in the order just mentioned. (3) A considerable degree of cerebrospinal involvement may be present in the latent period of syphilis without manifesting any signs or symptoms. (4) Such asymptomatic cases may become symptomatic later, and a study of the colloidal gold curve in these cases is of some value in estimating the ultimate prognosis of the case. (5) Comparing the large number of cases of primary and secondary syphilis in which positive findings are found with the relatively small percentage of late neurosyphilis as compared to total syphilitic incidence, we must conclude that a large number of early cases are in the nature of a meningeal roseola which is transitory in its clinical aspects. (6) The interpretation of the lumbar puncture findings particularly early in the incidence of the disease, constitutes a valuable guide in estimating the ultimate prognosis of the disease with regard to the integrity of the nervous system.

Industrial Lead Poisoning.—SHRE (*Jour. Am. Med. Assn.*, 1921, lxxvi, 835). Basing his opinions on findings encountered in a study of a large series of cases the author feels that certain symptoms have been unduly emphasized in the diagnosis of plumbism. Anemia is rare. Pallor of the skin is common, possibly due to peripheral vasoconstriction. Basophilia is unfrequent in acute cases and rare in chronic cases. The occurrence of hypertension is variable; it was practically absent in cases of plumbism occurring in pottery workers, whereas among "lead refiners" exposed to fumes it is almost universally present. Perhaps the difference in the form of lead to which the workers were exposed is responsible. Constipation is usual, though by no means constant. Diarrhea was a frequent complaint. A point of diagnostic value is the finding of an increased mononuclear percentage in the differential white blood cell count. This was almost invariably present. A lead line was noted in 90 per cent. of the cases. Peripheral nerve palsies were common. The importance of prophylactic measures (improved working conditions, personal hygiene, medical supervision of industries in which the lead hazard is present) is emphasized.

Serious Reactions to Repeated Transfusions in Pernicious Anemia.—BOWCOCK (*Johns Hopkins Hosp. Bull.*, 1921, xxxii, 83). From a review of the literature and careful study of three cases at the Johns Hopkins Hospital in which after a large number of transfusions there occurred extremely severe reactions following the transfusion of apparently compatible blood the author arrives at the following conclusions: "(1) In certain patients suffering with pernicious anemia who have been transfused repeatedly transfusion becomes self-limited because of the inadequacy of methods for selecting suitable donors. (2) The difficulty having once been discovered no attempt should be made to transfuse these patients. (3) The severe reaction is probably due to an antiphylactic manifestation, and not to hemolysis *per se*. (4) Blood-matching should be carried out with the greatest care, whenever possible the incubation period should be at least two hours, or longer. (5) Blood serum free from cellular elements may produce bone-marrow stimulation. (6) Members of Group IV cannot be regarded absolutely as universal donors."

SURGERY

UNDER THE CHARGE OF

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Hypophyseal Duct Tumors.—DUFFY (*Annals of Surgery*, 1920, lxxii, 532 and 725) says, in concluding a very excellent article on this subject, although there are embryological possibilities for growth of squamous epithelial neoplasms between the pharynx and the sella turcica, the great majority of such tumors develop from squamous epithelial embryonic rests of the hypophyseal duct either in the infundibulum or beneath the upper surface of the anterior lobe of the hypophysis. Of either origin the tumor usually presents above the sella. In view of the fact that a majority of these tumors are suprasellar in position from the beginning and that nearly all early assume this position, it appears that they are especially suitable surgically for an intracranial approach. In tumors which arise beneath the capsule of the anterior lobe the latter becomes flattened out below and a transphenoidal approach may destroy the entire anterior lobe of the hypophysis. The tumors derived from embryological remnants of the hypophyseal duct are quite different in structure from those derived from Rathke's pouch or cleft (between the anterior and posterior hypophyseal lobes). From the duct reliqui develop papillary squamous epithelial adamantinomatous tumors; whereas, from Rathke's pouch or the cleft develop simpler cysts lined by a single layer of ciliated cylindrical epithelium. The hypophyseal duct tumors histologically may be divided into three groups. Group I is that of the papillary cyst or intracystic papilloma which is histologically the most benign example of hypophyseal duct tumors. Group II includes the uncalcified or calcified adamantinomas (solid or cystic), the rarer tumors which closely resemble the basal epithelioma of skin, and the more complicated adamantinomas, the "autochthonous teratomas" of Ewing. The tumors of this group may show criteria of local malignancy, but do not metastasize. Group III comprises a very rare group of cases which show all the earmarks of malignant spinal-cell carcinoma and may metastasize extensively to the cervical lymphatics. The frequent occurrence of calcification in hypophyseal duct tumors is an important diagnostic fact. At variance with the statement of Jackson (1916) that roentgenography is usually negative, in each adamantinomatous tumor described by the writer the roentgenogram shows a suprasellar calcified nodule. The rarity of such calcified shadows in tumors of other types (adenomas, endotheliomas, etc.) makes such nodular shadows almost pathognomonic. The occurrence of bone in hypophyseal duct adamantinomas is not due to the presence of a congenital osseous anlage but is a result of activity on the part of the stroma,

apparently excited by the presence of calcium salts which have been deposited in the necrotic stratified epithelium. The mechanism of osseous change is apparently similar to that described by Nicholson for the same phenomenon in calcified cutaneous epitheliomas. Hypophyseal duct tumors of the infundibulum not infrequently break into the third ventricle. To the contrary, the tumors of the ependyma or choroid plexus of the third ventricle are very rarely present in the suprasellar region; this is explained by spread of the growth along the intraventricular paths of least resistance. During operations on suprasellar cysts in intimate contact with the floor of the third ventricle microscopic demonstration of squamous epithelium from the lining of the cyst will assure the surgeon that the cyst (or solid tumor) originated below the ventricle. A pathological fact of importance for the surgeon to appreciate is the intimate and delicate relation of such cysts with the floor of the ventricle, from which they are frequently separated only by a very thin membrane. The very frequent occurrence of the clinical syndrome of dystrophia adiposogenitalis (Frölich) in patients suffering with hypophyseal duct (squamous epithelial) tumors makes the pathological findings in the genital organs of two individuals of particular interest. In the uterus of a twenty-year-old girl there was an atrophic endometrium, almost equal to that of the senile type, associated with cessation of the process of ovulation (ovaries). The testes of a thirty-five-year-old man showed a marked atrophy of the spermatogenous epithelium.

Management of the Cervical Stump and the Round and Broad Ligaments when Performing Supravaginal Hysterectomy.—BISSEL (*Surg., Gynec. and Obst.*, 1920, xxxi, vi, 578), says if the action of the round ligaments, when these ligaments are anchored to the cervical stump, effects a change in the position of the cervix, then this change of position must be toward the symphysis and from the coccyx, and as the normal position of the cervix is in the immediate region of the coccyx, any marked change of its position toward the symphysis constitutes a displacement. If, when the round ligaments are anchored to the normally posed cervix, the position of the cervix after operation is found maintained, it is proof that the anchored round ligaments have had no influence upon the position of the cervix, as the direction of this influence, if any, must be toward the symphysis. A normal fascial diaphragm independently maintains the cervix in a normal position. Its action is constant and its resistance greater than that of the round ligaments, so that the influence of the anchored round ligaments upon the cervix must be *nil* when the fascial pelvic diaphragm is normal. If the posterior area of the fascial diaphragm is stretched by a retroposed corpus or tumor in the cul-de-sac of Douglas so as to advance the cervix toward the symphysis, shortening of the uterosacral or posterior ligaments is a more logical procedure than anchoring of the round ligaments to the cervical stump. If the entire fascial diaphragm has been injured sufficiently to permit of the cervix advancing and descending toward the vulva and an intra-abdominal removal of the corpus is deemed advisable, then the corpus should be removed without reference to the position of the cervix and the prolapse of the cervix with the vaginal vault corrected subsequently by lapping the fascia of the anterior vagi-

nal wall. No adequate proof has yet been offered to show that the influence of the round ligaments, when anchored to the cervix, enters as a factor, in the slightest degree, in maintaining the normal position of the cervix nor in restoring a displaced cervix to normal. Prolapse of the cervix does not and cannot occur after supravaginal hysterectomy, if previous to the operation the fascial diaphragm is uninjured and the cervix is in normal position.

Renal Hematuria as a Symptom of a Perinephritic Condition of the Kidneys.—YOUNG (*Surg., Gynec. and Obst.*, 1920, xxxi, 478) says that of 1300 cases treated in the house service of the Genito-urinary Department of the Massachusetts General Hospital, 40 per cent. had a history of gross hematuria at some time or other in the history of the disease. The cause of renal hematuria can be demonstrated in all but a very small proportion of cases. Kidney bleeding of unknown origin has been known to be enough to threaten life and require nephrectomy. A horseshoe kidney, a slightly movable kidney, a varix of a renal papilla may occasionally exist without the possibility of positive pre-operative diagnosis. In a few instances the split function may show considerable damage on the bleeding side and the pyelogram a considerable deviation from the normal, a combination which should require exploration; but these cases are very rare and operation as a routine exploratory procedure in cases of hematuria of unknown origin is unwise, as there is no assurance that it will have any effect on the progress of the bleeding. In a fair number of these cases a nephritis has been proved to be the cause of trouble. It is reasonable to believe that in a majority of these cases there is an early unrecognized nephritis or a perinephritic condition which can be, and probably often is, the cause of hematuria, and that this condition may or may not go on to a progressive damage of the kidney, depending on conditions which we do not as yet understand. In certain of these cases the primary focus of damage can be recognized, and when eliminated will prevent the later development of the disease.

Blastomycosis.—MOORE (*Surg., Gynec. and Obst.*, 1920, xxxi, 590) reports a case of cranial blastomycotic infection. Little is to be found in our modern text-books on the systemic involvement of various organs of the body by this infection. Moore's case received the infection through a puncture wound as many of the cases do. The infection in this case was probably introduced through the mouth from the splinters habitually carried in the mouth. The treatment of the case was hardly radical enough in destroying the various recurring foci of the disease. The eye should have been sacrificed earlier, and radium used in the orbit as the roentgen ray was apparently the best agent used in the treating of the lesions on the face and neck. The disease remained more or less local for a long time notwithstanding its tendency to spread through the lymphatics and become systemic. No organisms were obtained either from the urine or sputum, nor did we succeed in getting a culture from the blood. The infection of the brain was possibly through the ophthalmic vein or through the veins of the scalp

and emissary vein through the skull. The study of the organisms in the different lesions and tissues showed a considerable variation in their size; those from the abscesses of the face, neck, and orbit, showing the large forms, while no large forms could be found either in the pus or the tissue from the brain. There are many budding forms of the organisms, but no evidence of endosporulation, as in coccidiodes.

PEDIATRICS

UNDER THE CHARGE OF

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A Clinical Classification of Diarrheas.—ROYSTER (*Arch. Ped.* September, 1920) classifies the diarrheas of early life as follows: Food injury (acute) from overloading the digestive tract, particularly the stomach, with proper food; the accidental administration of an excess of one or more food elements in a bottle baby's formula, either fat, carbohydrate or protein nervous diarrhea from sudden overheating or sudden chilling, excitement or fear, improper or indigestible food; food injury (chronic) from the habitual administration of too large quantities of one or more of the normal and proper food elements or mixtures too strong in all elements; fermental diarrhea; infectious diarrheas due to the dysentery group of organisms, the gas bacillus or other organisms. An effort was made to ascertain what relation existed between the onset of summer diarrhea and the temperature and humidity. Last summer the warm weather was late, its onset not having been well established before June 12, which was two or three weeks later than usual. The incidence of diarrhea was correspondingly late in its appearance. The mean of the observations of the local weather was taken as the only practical record. The temperature was averaged each day from the highest to the lowest. The relative humidity was observed at 8 A.M. and 8 P.M., and an average taken. The incidence of cases exactly followed these curves. It was of great interest to note the height of the incidence on the day following the height of the temperature.

Effort Syndrome in Children.—KERLEY (*Arch. Ped.*, August, 1920) reports several cases which are given as illustrations of the condition to which this name is applied. As the most prominent symptoms involve the circulatory and nervous systems, it has also been called "neurocirculatory asthenia" or "neurocirculatory myasthenia." The chief cause has been found to be infections from the tonsils, teeth and other foci. The child who may later become a member of this group presents a typical history, which tells of absence of capacity for sus-

tained effort either mental or physical. They are usually backward in school although they are intelligent, but seem unable to apply themselves sufficiently to keep up with the average. They are also physically unfit for the usual activities of childhood. They tire readily and prefer to be spectators rather than to participate actively in the games and amusements. They are not ill and usually it is impossible to show evidence of disease even under the most careful and rigid examination. One of the distinguishing characteristics is lack of nervous control. Therapeutically the results have been discouraging. They do fairly well in non-strenuous occupations. It is unusual to find children of this type the offspring of vigorous young persons. In a great majority of cases they are the offspring of a weakly mother with little resistance and of lessened endurance capacity. A strong vigorous mother will do much to offset the unfavorable influence on the progeny of a weakly male. The progeny of vigorous males is greatly handicapped by an inferior mother.

Bodily Mechanics.—TALBOT and BROWN (*Am. Jour. Dis. Children*, September, 1920) report a number of cases of cyclic vomiting and other obscure intestinal conditions as the result of poor posture. They think that faulty bodily mechanics was responsible for a great loss of efficiency among adults during the war. Correcting it changed inefficient men into efficient soldiers. It is a condition common to all ages, and it is surprisingly prevalent. It is easily corrected and can be most economically done during childhood. It is responsible for most instances of diminished power of digesting fats in children. It is the cause for a certain amount of chronic constipation. It is the background and probably the cause of many, if not of most, of the cases of recurrent vomiting. In many instances the symptoms of acute abdominal pain in children, when associated with chronic constipation, is due to poor bodily mechanics. These symptoms are often so severe that they are confused with those of acute intestinal obstruction due to other causes. In the cases reported, in which the faulty postures have been corrected in conjunction with other treatment, the patients have shown a more speedy recovery than in cases without correction.

The Schick Test, Its Control, and Active Immunization Against Diphtheria—BLAU (*New York Med. Jour.*, August 28, 1920) in his work used the capillary outfit as furnished by the New York Health Department. The technic is as follows: Break off one end of the capillary tube not having the black mark. Push the broken end through the neck of the rubber bulb until it punctures the diaphragm and enters the cavity of the bulb. Break off the other end of the tube. Expel the contents into one of the vials containing 10 c.c. of saline solution by placing the index finger over the opening in the larger end of the bulb. Rinse the capillary tube by drawing up saline solution several times. Cork the saline vial and shake the dilution. Inject 0.2 c.c. of the diluted toxin, representing one-fiftieth minimum lethal dose for the guinea-pig, intracutaneously on the flexor surface of the left forearm. The control test is proceeded with in the same manner using the capillary tube with the black mark, and making the injection into the flexor surface of the right forearm. The reactions should be observed at the

end of twenty-four and forty-eight hours, basing the final judgment upon the last reading. The positive reading becomes apparent at the end of from one to four days, averaging at the end of the second day, at a time when the pseudo-element of the reaction has disappeared. It consists of a definitely circumscribed area of redness, from 1 to $2\frac{1}{2}$ cm. in diameter, with a superficial scaling and a beginning brownish pigmentation. A strongly positive reaction will occasionally show vesiculation of the surface layers of the epithelium. The reaction gradually disappears in from one to four weeks going through various stages of scaling and pigmentation. After about two weeks a distinct brownish area is seen at the site of the injection. Occasionally a pseudo-reaction is manifested. This shows an indefinite area of redness of varying size, surrounded by a secondary areolar which shades into the surrounding skin. The pseudo-reaction appears earlier than the positive reaction in from six to eighteen hours, reaches its height in from twenty-four to thirty-six hours, and disappears by the end of from two to four days, at the time when the positive reaction becomes apparent, and may have a poorly defined area of pigmentation but no scaling. The combined reaction shows a positive and a pseudo-reaction in one. The positive element of the reaction becomes apparent at the end of from two to four days, at a time when the pseudo-reaction has disappeared. The appearance of the positive element is the same as the positive uncombined reaction. The appearance of the pseudo-reaction is the same as the uncombined pseudo-reaction, and resembles the reading at the site of the control test if there is a reaction at the control, with which it should be compared. The doubtful reaction is where the reaction is not typically positive negative, nor a pseudo-reaction. In these cases the reading should be made as positive. In the control reaction nothing is seen, but occasionally it shows a pseudo-reaction. The Schick test is positive between the ages of one and four years in about 32 per cent. of normal children. It is positive in a slightly larger proportion of measles cases, in twice as many scarlet fever cases, and in nearly three times as many cases of poliomyelitis. After the sixth year the proportion of positive reactions rapidly decreases, being positive in about 10 per cent. In adults 85 to 95 per cent. of the tests are negative. For active immunization a solution of undiluted toxin and antitoxin is used.

The Dietetic Treatment of Summer Diarrhea.—GRIFFITH (*Arch. Ped.*, August, 1920) says that the correct management of the diet is the most important factor in treatment. The first and the most important step is the immediate and complete withdrawal of food at the beginning of the attack. It is advisable to instruct mothers that with any digestive disturbance whatever, food should be withdrawn without waiting to call the doctor. The second step is the removal of any food already in the intestines. Castor oil or magnesia are advised to accomplish this. If there is vomiting, it may be necessary to wait for its subsidence before giving the purgative. A large intestinal douche can, however, be given at once. The length of the period of starvation depends upon the case. A breast-fed baby may be kept from suckling for twenty-four hours. Bottle-fed babies usually require a longer time. Water should be given freely, and it is often a great relief to the mind of the mother, if she is allowed to use barley water. So long as the fever remains

showing that an infection is still present, resumption of the milk diet should be delayed. When it is started, it should be given in small quantities diluted and preferably skimmed, and the return to the original strength should be made gradually. An excess of fat or sugar may cause diarrhea. Broths thickened with starchy substances or even thick porridges are of great value when the time for the return to food has come and the action of the milk is feared. In obstinate cases it is sometimes best to abandon the milk mixture and to use whey, casein milk, buttermilk, or the like. The thick gruels are very valuable as foods. On account of the starch, it is not advisable to continue their use over long periods. On account of the danger of relapse and recurrence restriction of the diet should be continued for the duration of hot weather. Gain of weight in these cases becomes of minor importance for the time. Acidosis is one of the great dangers during diarrhea.

OBSTETRICS

UNDER THE CHARGE OF

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The Prophylactic Forceps Operation.—DELEE (*Am. Jour. Obst.*, October, 1920, No. 1) contributes a paper in which he urges that many patients be delivered by the use of forceps without waiting for spontaneous expulsion. His method is as follows: When the pains are well established and cervix partly dilated, morphin-scopolamin are given and $\frac{1}{400}$ scopolamin given several times afterward. The patient's room is darkened and suggestion is employed. When the cervix does not dilate 15 grains of chloral and 40 grains sodium bromide are given by rectum, or gas and oxygen administered. It is important to obtain complete spontaneous dilatation of the cervix as slowly as possible; not only does the cervix dilate but the paracervical tissues retract which is most important and cannot be imitated by artificial means. When the head has left the cervix and rests between the levator and stretching the facia, ether is given to complete anesthesia and perineotomy is performed. The fetal heart sounds are carefully watched and forceps applied and patient delivered. Pituiglandol is often injected as the placenta passes out through the vulva, aseptic ergot is also injected if there is any hemorrhage. The operator waits five to ten minutes before delivering the placenta. If necessary the operator disinfects his gloves carefully and if the placenta is not visible inserts the left hand into the vagina and lower segment, palm up, while the uterus is pushed down on the placenta and the placenta then slides along the hand. If there is bleeding more pituitrin is given and $\frac{1}{4}$ grain of morphin and $\frac{1}{200}$ scopolamin is then administered to reduce the quantity of ether required for repair work, prolonging narcosis for many hours postpartum and abolish the memory of the labor as much

as possible. The cervix is then repaired and also the perineum and pelvic floor. The writer illustrates his conception of the anatomy of the parts and when this paper was presented, employed models to illustrate his idea. For this method the writer claims that it saves the woman the debilitating effects of suffering in the first stage and the physical labor of the second stage; but little blood is lost by this procedure. This method preserves the integrity of the pelvic floor and other tissues and prevents the results which follow lacerations. The brain of the child is protected from injury and from the effects of prolonged compression. In the hands of those not expert, this method might produce bad results. In a mother infected before labor complications might arise. The writer has had no mortality; mothers and children have done well. It is interesting to note that the method of version at the end of the first stage of labor proposed by Potter of Buffalo is condemned by the writer. He states while in Potter's hands the operation of version is safe, in less skilful hands very bad results will follow. In his mind, however, the same argument applies with less force to his recommendation of the operation of prophylactic forceps. This paper was presented before the American Gynecological Society and the majority of opinion was strongly against the adoption of this method in all cases and by all those who practise obstetrics. It was recognized as a procedure appropriate for experienced operators only.

Cranial and Intracranial Birth Injury.—BAILY (*Am. Jour. Obst.*, October, 1920, No. 1) calls attention to the fact that a considerable proportion of stillbirths and early deaths are due to injury to the head of the child. In a few instances the prompt application of treatment might lower the mortality and morbidity. The mechanism of the injury has been described and illustrated. The veins of the cortex have little support as they enter the sinuses and hence pressure may readily rupture these vessels. In deformed pelvises the head will mold unnaturally and undue pressure is inevitable. The posterior parietal bone may often produce severe injury. When the skull is fractured there is usually rupture of the meningeal vessels, although this condition seems to be rare probably because the dura is loosely attached to the bone in the newborn. A bad application of the forceps or excessive force might produce such a result. Bleeding from surfaces of the cortex is often retained beneath the pia and if near the cortical centers may produce considerable damage. Hemorrhage into one of the ventricles may occur from rupture of the corpus callosum. The 40 cases proved by autopsy of cervical hemorrhage in infants, occurring at the Manhattan Maternity Hospital, are described in detail. Of these but 10 were not stillborn, 1 lived twenty minutes, another thirty, 1 three hours and others from fourteen hours to four days. But 2 of the children were delivered by forceps, 2 premature and 5 normal births. In the entire series 9 were forceps deliveries, 11 breech extraction, 5 preceded by version, 1 Cesarean case and 17 normal deliveries. The hemorrhage was diffuse in 18, especially marked under one bone in 11, diffuse, not in ventricle in 2, ventricle alone in 2, diffuse meningeal hemorrhage with thrombosis of the sinus in 1, 2 in the cerebellum, 2 in the pia mater, 2 in the dura mater. Five recent

cases of cranial and intracranial injury are reported in detail, three of them treated by operation with recovery and two dying without operation. In one of these a large osteoplastic flap was produced. In reviewing the literature of the subject it is found that results from decompression operations in infancy have not been really good. In some series the mortality has risen to 50 per cent. The raising of the depressed bone by piercing the bone with a sharp instrument and then pulling it up as recommended by Tweedy, is considered a makeshift.

American Journal of Obstetrics and Gynecology.—The publication so long issued by William Wood & Company, of New York, was by them discontinued some months previously. Obstetricians and gynecologists were not content, however, without a journal devoted exclusively to this branch of medicine. Dr. George W. Kosmak, editor of the *American Journal of Obstetrics*, with the assistance of others, formed an editorial board and the new journal was adopted as the official organ of the American Gynecological Association, American Association of Gynecologists and Obstetricians and Obstetrical Societies of New York, Philadelphia and Brooklyn. It is edited by Dr. George W. Kosmak, of New York, with Dr. Hugo Ehrenfest, of St. Louis, as associate editor. The publication of the journal was assumed by the C. V. Mosby Company of St. Louis. The first issue of the journal is printed on good paper with clear type and illustrations well produced. With the endorsement of American obstetricians and gynecologists and under the control of its able editor and editorial board this journal should have a most successful career.

The Function of the Corpus Luteum.—OCHSNER (*Surg., Gynec. and Obst.*, November, 1920) contributes further observations upon the function of the corpus luteum. He quotes the observations of veterinarians and describes 9 cases among human beings, where he has operated and removed the false corpus luteum. The health of the patient was greatly benefited and in many cases sterility was relieved. He quotes 2 cases illustrating the importance of avoiding, in operations, injury to the true corpus luteum. Observations seem to show that such injury is followed by abortion. His investigations indicate that an unabsorbed false corpus luteum prevents ovulation and is a common cause of sterility and that when such a false corpus luteum is removed by excision or expression menstruation occurs as a result. While this is true of the false corpus luteum if the true corpus luteum is excised or ruptured during the early months of pregnancy, abortion follows and this must be considered as one of the common causes of early abortion. It is interesting to note that injury to the true or false corpus luteum may simulate ruptured ectopic gestation.

Abdominal Pregnancy with Living Fetus.—MAURY (*Surg., Gynec. and Obst.*, November, 1920) has collected 29 cases of abdominal pregnancy in which the fetus was living at the time of operation. These occurred between 1909 and 1918. In 62+ per cent. the diagnosis was made before operation. In the whole number 73 were operated upon, 55 recovered and 18 died, a mortality of 24.6 per cent. There

has been but little improvement in the maternal mortality in recent years and in fatal cases death resulted from hemorrhage, sepsis or both; embolism, pneumonia and intestinal obstruction were also causes of death. The infant mortality was between 40 and 50 per cent. In a number of cases the child was deformed (usually some form of talipes), and the rate of deformity was about one-third of all the children. This did not seem to result in congenital cases, but from pressure to which the child's limbs were subjected in its unnatural position within the abdomen. About one-fourth of them gave history of premature rupture while the remainder had not been diagnosticated. A great majority suffered from pain in the abdomen which sometimes caused nausea and vomiting and frequently produced faintness and syncope. In about one-fourth of the cases irregular bleeding from the uterus had occurred and in one patient menstruation had been regular up to the time of operation. The placenta was usually attached to the pelvic organs, in 2 cases to the liver. In some there was a pedicle which could be ligated like the pedicle of a cyst. In some cases the tissue was so situated that the placenta could be removed together with the organ to which it was attached. Statistics show that if the placenta can be completely removed the mortality is very much less than where it is left or partially removed. There is no constant statement concerning the size of the uterus which seems to have varied greatly in different patients. As regards treatment these patients may be divided into three classes: (1) Those where the condition is not recognized and the patient goes into spurious labor with failure to deliver herself; (2) those where diagnosis is made but where the patient is so comfortable that she prefers to go on to as near term as possible without operation; (3) those who suffer so much from pain, faintness, hemorrhage or toxemia that they seek medical aid and should receive operation at once. While the first class are most numerous, as they do not often come to the physician, they are of less practical interest than the third. The majority of medical opinion favors operation in abdominal pregnancy if possible during the life of the fetus. It has been found that the further the woman is from term the greater are her chances of developing serious complications, the first half of pregnancy is more dangerous than the second. In those patients who are fairly comfortable, if they are seen before seven and a half months, operation should be done in the interest of the mother, if they are seen after that time, if they are in good condition and doing well and can be kept under observation, operation may be deferred until the death of the child. In each individual case the operator must decide whether he will remove the placenta or allow it to remain. Complete removal has given a maternal mortality of 10 per cent. while the mortality has risen to 40 per cent. in cases where the placenta was allowed to remain. The decision, however, cannot be based on statistics alone, but each case must be examined and determined upon its individual merits. When a pedicle can be ligated, the removal is simple. When the placenta grows from an organ which can readily be removed, this is also favorable, but when the placenta has developed on the liver or mesentery or is plastered on the wall of the pelvis, decision is difficult and there is great danger of hemorrhage at the time of operation or subsequently.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Lessons Taught by Measures for Control of Venereal Diseases.—PIERCE and WHITE (*Jour. Am. Med. Assn.*, 1920, lxxv, 1133) state that closer coöperation should be developed between state boards of health and the Public Health Service, and between state boards of health and local health officers to encourage a uniform method of venereal disease control throughout the United States. It adds much to the effectiveness of any public work to adopt and put into practice a uniform procedure. Uniformity impresses the fact on those that come into contact with the work that definite knowledge is possessed by health authorities. Health authorities should recognize the important part unofficial agencies may take in venereal disease control work if the activities of voluntary organizations are properly supervised. The moral, social and economic phases of venereal disease control work can be materially advanced by organizations and citizens interested in these particular problems. The results so secured will reduce the burden of the control of venereal diseases now largely borne by health officials. Progress will be materially advanced when the medical profession takes more interest in control of venereal disease than it does at the present time. Members of the medical profession should naturally assume leadership in all plans for promoting public health, and there certainly is urgent need for every physician to renew and maintain his interest in all phases of the present program for venereal disease control. Every medical college should provide better facilities for preparing future physicians to have a greater knowledge of the venereal diseases. There is need for a wider development of follow-up work in connection with treating persons infected with venereal diseases. A follow-up staff should be a part of the personnel of every venereal disease specialist. The duties of such a staff are to keep track of patients needing further treatment; to determine sources of infection; to see that precautions to prevent the spread of infections are being observed by patients; to discover other cases among the associates and members of the family of infected persons, and to carry on sociological and psychologic observations that will be of value in limiting the further spread of venereal infections. The question of equal treatment of both male and female infected persons must be placed on a scientific and equitable basis. All persons of either sex infected with either gonorrhea or syphilis are a very definite menace to the health of the community in which they reside; and unless infected individuals can be depended on to observe

precautions to prevent the spread of their infection to others, they should be placed under either modified or absolute quarantine restrictions. Careful and thoughtful consideration must be given by physicians, teachers, psychologists and intelligent parents to the question of deciding on the material to be used and the methods of applying instruction to questions of sex and venereal disease prevention. There is no phase of public health work which is attended by greater difficulties and which presents so many various aspects for consideration as does the problem of venereal disease control. Every one who has had actual experience in carrying on any part of the program has been greatly impressed with the tremendous scope and possibilities of the work and deeply realizes the necessity for not only continuing, but for greatly expanding the present plan of action. It can be stated without qualification or doubt that the great mass of intelligent citizens of the United States are deeply interested in this problem and will give their unqualified support to health officers, physicians and others attempting to meet their responsibilities for preventing the spread of venereal diseases.

An Epidemiological Study of an Endemic Focus of Leprosy.—BOYD and FOX (*Public Health Reports*, 1920, xxxv, 3007) have studied leprosy in a Gulf Coast city where the disease has prevailed for about thirty years. The investigation embraces 45 cases, at least 36 of which were infected locally. Males predominated, as in other leprosy foci. The age incidence showed the second decade to furnish more cases than any other, and residence in the focus of from eighteen to twenty years prior to onset was the rule. The tuberculous and mixed types formed the large majority of the cases. It is suggested that not all cases in the focus have come under observation. It seems likely that there are several fairly well-defined foci, other parts being relatively free. Persons of German birth or parentage seem especially susceptible. A history of contact with known lepers was obtained in about half of the cases. The possibility of insect transmission is discussed, but not regarded as likely. There is no official control of leprosy in the focus.

Information Concerning Rat Surveys and Rat Proofing.—The Public Health Service (*Public Health Reports*, 1920, xxxv, 2615) in this paper considers first the disadvantage of rat infestations from the economic, commercial and sanitary points of view, which is followed by a discussion of rat surveys for the detection of plague infection. The number of rats examined should be at least 1000 for every 10,000 of the human population, and a preliminary survey should be made in order that the most promising locations shall be trapped. The rat-proofing of buildings by elevation, to prevent harboring underneath, and by the use of concrete for floors and area walls is described, and model ordinances are presented.

Biological Investigation of California Rice Fields Relative to Mosquito Breeding.—PURDY (*Public Health Reports*, 1920, xxxv, 2556) made a study of the breeding of malaria-carrying mosquitoes in rice fields in California, contrasting the findings with those secured from a similar investigation in Arkansas. The most striking difference

was that while in Arkansas rice fields furnished many *anopheles* they furnished few or none in California. Indeed, no mosquitoes were found to breed in large numbers in the California rice fields. The author expresses the opinion that it is not practicable to control *anopheles* by control of the food supply of the larvæ on account of the diversity of organic matter, living or dead, which serves for the larvæ. The normal enemies of larvæ are described, particularly the top minnows (*Gambusia*) that have been so much used in mosquito control. The prevalence of the various mosquito found, and their seasonal distribution, are described.

The Role of Live Stock in Malaria Prophylaxis.—The U. S. Public Health Service (*Public Health Reports*, 1920, xxxv, 2462) quotes from ROUBAUD (original *Annales de l'Institut Pasteur*, 1920, vol. xxxiv) in reference to the possibility that domestic live stock may play a role in the prophylaxis of malaria. It has been noted in parts of western Europe that malaria may disappear without the extinction of malaria-carrying mosquitoes. It is asserted that in certain localities the *anopheles* prefer the blood of cattle, horses, etc., to that of man. It is proposed that advantage be taken of the habits of the *anopheles* and animal prophylaxis be made a part of the program of malaria control.

The Medical Profession and Notifiable Diseases.—BOWMAN (*Public Health Reports*, 1920, xxxv, 2503) details the reasons for requiring reports from medical men on the prevalence of certain diseases. He states that it is necessary to have compliance with the laws and rules on the subject in order that suitable control measures may be taken in the case of diseases that may be made the subject of sanitary control, and that in other cases the reporting is necessary to secure further knowledge of diseases about which we know too little now to be of practical value in their suppression. The following summary is presented: No disease has been placed on the notifiable list arbitrarily or by chance, but each for some definite reason. It therefore behooves every doctor to report every case of each notifiable disease for the following reasons: That the proper authorities may be informed and prevent further spread—That the information gained may be available as evidence of the need of public health work—That further knowledge may be gained as to the etiology and spread of diseases under conditions of which we now have no data—and That the location of areas where certain diseases prevail may be known when it is possible to undertake special measures for their eradication.

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